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*Paulo Matos da Costa*
Editor Chefe da Revista Portuguesa de Cirurgia

https://www.youtube.com/watch?v=lSVF8w-YKPw

Estimado Colega

A atual Direção da nossa Sociedade dirigiu-me o honroso convite para ser o Editor da Revista Portuguesa de Cirurgia.

Após sondar um grupo de Colegas, que muito prezo, e que aceitaram entrar neste desafio comigo, pensei que seria possível.

Como podem verificar, cada membro da equipa Editorial já deu provas da sua distinção e empenhamento nas responsabilidades que assume e nas aventuras em que se mete.

No momento em que me dirijo a si, tenho dificuldade em quantificar qual das duas qualidades é mais necessária para Editar regularmente esta Revista. Será o empenhamento ou o aventureirismo?

Não vamos desenterrar o passado, vamos tentar reanimar o que ainda não estiver irremediavelmente perdido. Mas o que está perdido é demasiado.

Iniciámos a recuperação da indexação da Revista Portuguesa de Cirurgia na Plataforma SciELO e retomámos a candidatura ao Registo DOI na FCT.

Estes procedimentos foram duas das nossas principais preocupações e ambos os processos pensamos que não estão longe de ser levados a bom porto. A partir deste número todos os artigos tem DOI.

Estamos a estudar as candidaturas possíveis a outras bases de arquivo e referenciação de artigos que garantam uma boa visibilidade aos trabalhos publicados.

A todos os Autores, que viram os seus trabalhos enviados para publicação sem resposta durante um tempo mais dilatado, queremos reafirmar que já iniciámos os processos de revisão e já começámos a informar o resultado dos comentários tecidos pelos Revisores.

Compreendemos que muitos Autores já tenham publicado noutras Revistas ou já não tenham interesse em rever textos ultrapassados pelos anos.

O nosso compromisso, para que o processo de publicação entre na normalidade desejável, fica aqui expresso em nome de toda a equipa Editorial.

Os trabalhos, após aceitação e edição, serão publicados *online ahead of magazine compilation*.

Como lhes será atribuído um DOI, passam a ser imediatamente citáveis.

A Revista, por ser exclusivamente publicada online, tem que aprender os caminhos desse formato. As potencialidades são quase ilimitadas.

Interação e imagem convivem naturalmente com a edição online.

Os melhores vídeos que cada um tem realizado podem ser editados e publicados com o mesmo rigor que os trabalhos *in extenso*, como os que incluímos neste número.

As Normas de Publicação estão a ser revistas. Antes de começar a preparar o seu manuscrito ou vídeo preste-lhes a atenção devida, para evitar atrasos na análise e na publicação.

Os trabalhos de investigação são um dos elementos *core* de todas as revistas científicas, e é naturalmente o nosso. A investigação em cirurgia desde sempre se focou num vasto leque de modelos. O que hoje chamamos investigação clínica, laboratorial e de tradução (*translation*) há décadas que faz o encantamento dos cirurgiões – não usávamos era estas designações, mas o *bench to bed* já estava na mente dos cirurgiões que hoje chamados "gigantes".

A revista está muito interessada em publicar Casos Clínicos. Privilegiaremos o formato de apresentação e discussão da linha condutora do diagnóstico, ao tratamento e ao prognóstico, isto é, o pensamento, as incertezas do manejo do caso, que é o desiderato da publicação de casos clínicos. A bibliografia deve circunscrever-se a substanciar esta linha condutora. Fazer uma revisão da literatura a propósito de um caso clínico retira a vivacidade e o interesse do exercício de demonstração das etapas clínicas, que tanto interessam os nossos leitores.

As revisões sistemáticas da literatura, que se enquadram na linha editorial da Revista, devem seguir as normas atualmente aceites pela comunidade científica.

O artigo de opinião, solicitado pelos Editores a uma figura consagrada, ou muito ativa num qualquer campo da cirurgia, dispensa, por definição, essas regras de análise da literatura.

Por iniciativa própria, por sugestão da Direção da Sociedade, dos Capítulos e outras, podemos desencadear a publicação de Suplementos. Os trabalhos com "resumos alargados", aceites por revisores para apresentação nos nossos Congressos são um bom exemplo. Vamos analisar os trabalhos que não puderam ser apresentados no Congresso 2020, que a Direção se viu obrigada a cancelar. Naturalmente que a nossa atenção se focará nos Resumos Alargados e não nos Resumos submetidos inicialmente.

Muitos dos nossos Sócios têm desenvolvido um trabalho de excecional qualidade como tutores/orientadores de Teses de MIM. Esse esforço pode ser perfeitamente compaginado com a linha editorial da Revista. Importa que a apresentação se enquadre nas Normas de publicação, para serem atempadamente encaminhados para a revisão por pares (duplamente cega, como acontece com todos os outros trabalhos). Como nota acrescento que a obtenção das classificações mais altas, para serem atribuídas a esses trabalhos, em algumas Faculdades, é exigida a publicação numa Revista com Revisores.

Esta Revista terá que ser um "fórum" de encontro dos nossos Internos. Estamos seguros de que vamos encontrar a forma e as vias necessárias para os ajudar a cumprir os seus sonhos e a publicar bons trabalhos. É uma prioridade deste grupo Editorial.

O alinhamento da revista vai seguramente sofrer adaptações ditadas pela experiência e pelas opiniões que vierem a ser reportadas.

Após o "Edital" teremos a "Página da Direção".

Como abertura serão apresentados trabalhos solicitados pelos Editores que devem versar temas da atualidade. Para esta secção, "Editor' Corner", pensamos poder contar com perspetivas de diferentes ramos do saber ou experiências relevantes.

Os trabalhos submetidos para publicação passaram a integrar as secções seguintes, de acordo com o respetivo conteúdo: "Artigos de Revisão", "Artigos de Investigação", "Casos Clínicos", "Imagens para Cirurgiões" e "Vídeos".

Disfrute deste seu número 47 e envie-me os seus comentários e sugestões.

No Editor' Corner vai encontrar uma reflexão sobre a vivência da pandemia numa das cidades mais fustigadas pela sobrelotação/falência dos meios disponíveis para prestar cuidados aos doentes, Brescia. Um cirurgião duplamente no meio do furacão.

A atual necessidade de modificarmos os nossos procedimentos de "atender" os doentes fez-nos inventar novas soluções para que as "consultas" não presenciais fossem bem acolhidas pelos doentes e eficazes. Um artigo de opinião pareceu-nos de atualidade e interessante.

O grande salto que demos da macroscopia para a célula é seguramente pequeno comparado com o que estamos a dar, da célula cancerosa para o seu interior (genes) e para o meio envolvente (estroma) no tumor e nas metástases. Trazemos uma visão atual sobre a nova realidade das metástases líquidas, uma perspetiva que vai entrar na nossa prática mais cedo do que podíamos pensar há bem pouco tempo.

Dos artigos submetidos pelos Autores selecionámos uma limitada amostra que interessará pela diversidade e qualidade.

A introdução dos vídeos foi uma aposta que estamos seguros vai captar a atenção.

A Revista Portuguesa de Cirurgia é sua. Contribua para a prestigiar. Nós orientaremos essas dádivas, garantiremos a qualidade e lutaremos por uma referenciação condigna.

Vamos vitalizar a Revista.

Aceite os meus cumprimentos e de todos os Editores.

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# Página da Sociedade Portuguesa de Cirurgia

*Gil Gonçalves*
Presidente da Sociedade Portuguesa de Cirurgia

A Sociedade Portuguesa de Cirurgia (SPCir) a caminho de meio século de existência, deve adaptar-se aos desafios que a especialidade enfrenta, reformulando o seu plano de ação e intervenção, com uma visão moderna, com objetivos centrados na Formação creditada, no incentivo à investigação e publicação.

O acesso mais facilitado ao saber e ao conhecimento tornou mais fácil a aquisição de competências nas diversas áreas. Mas nem tudo é informação credível, pelo que a filtragem em muitas situações é complexa e a sua translação potencialmente perigosa para os doentes. A assimetria na formação, pela amplitude e heterogeneidade das instituições responsáveis pela mesma, obriga à necessidade de fomentar a boa formação e este terá de ser um papel determinante da SPCir.

A SPCir irá dar início a um programa formativo nacional para internos e cirurgiões. As Sociedades Científicas têm o dever de colaborar ativamente com os serviços na formação em cirurgia, aportando um cunho de qualidade científica creditada. Os diversos patamares de atuação permitirão abrir um leque grande de opções formativas, mas em que a SPCir, através dos seus órgãos próprios, terá um papel central. Se é certo que trará algum trabalho acrescido, estamos certos que a distribuição de tarefas, tanto organizativas como executivas, permitirá que o programa se inicie e se desenvolva, na medida necessária, ao longo da vida da Sociedade.

Foi criada na direção uma comissão de formação composta por cinco elementos, a que compete propor o programa formativo para o Internato e coordenar e analisar as diversas propostas formativas formuladas por Capítulos e Comissão de Educação e Serviços.

Aos capítulos da SPCir foram definidas competências que lhes permitam cumprir a sua atividade e objetivos, nomeadamente desenvolver ações formativas na sua área, incentivar e promover a investigação científica na respetiva área de interesse, assessorar a direção na creditação de eventos científicos específicos em cada área, assessorar a direção na elaboração ou validação de documentos de referência, nomeadamente normas de orientação clínica e linhas de orientação, que possam auxiliar os cirurgiões de cada área a estruturar o seu desempenho clínico de acordo com a *legis artis* e colaborar com a direção na organização do Congresso Nacional. Dada a limitação estatutária de permitir três elementos para cada capítulo, criou esta direção uma

comissão de educação que garante uma maior amplitude de cirurgiões a colaborar dentro dos capítulos, com funções em tudo semelhantes.

Definido que está o programa base para a formação do Internato para os três primeiros anos, segue-se uma calendarização do mesmo, com a elaboração dos conteúdos, a definição do modo de apresentação, a sua validação pelos capítulos e comissão de educação (outubro de 2020) e a sua aplicabilidade a partir de Janeiro de 2021. Esse programa será oportunamente anunciado.

Aos serviços de cirurgia geral será solicitada a sua colaboração ativa noutro patamar formativo, que constará da organização de *observerships/preceptorships* para internos (consoante o ano de internato) e especialistas, com programa validado e creditado pela SPCir.

A realização da reunião anual do capítulo é um objetivo a alcançar, permitindo a discussão concentrada num evento de temas específicos, de atualização de conteúdos nas áreas respetivas, deixando para o congresso nacional temas transversais a toda a cirurgia geral. Estas reuniões anuais seriam organizadas rotativamente pelos vários serviços que colaborariam com o respetivo capítulo na definição do programa.

A adaptação progressiva da formação em cirurgia geral ao que está definido pela União Europeia de Médicos Especialistas deve ser um objetivo, para o qual a SPCir estará disponível, colaborando com o Colégio de Especialidade da Ordem dos Médicos.

Trata-se de um programa formativo que terá de ser construído de forma gradual, adaptando-se a novas realidades, a novas propostas, que devem partir de toda a comunidade cirúrgica. A SPCir será uma boa ouvinte para que se possa caminhar de forma consistente, moderna e creditada.

Junho de 2020

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TESTEMUNHO

# COVID19 NIGHTMARE: THOUGHTS OF A SURGEON FROM THE CENTER OF THE STORM

## O PESADELO COVID 19: REFLEXÕES DE UM CIRURGIÃO NO CENTRO DA TEMPESTADE

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*"It is* necessary *that the heroic becomes daily and that the daily becomes heroic"*

(John Paul II, 23 March 1980,
Homily on San Benedetto da Norcia)

FIG. 1 – **The night view of Brescia Cathedral, 17th century AC.**

Brescia is a rich roman town in northern Italy with about 200,000 inhabitants (Fig. 1), capital of an industrialized and hardworking province of more than 1,000,000 people. At the beginning of 2020, the political and social attention was addressed to the redevelopment of the historic center, to the social integration of a non-EU citizens rate – amongst the highest in Europe – to the technological innovation required by international competition, to the difficulties of the football team, which was

Fig. 2 – **St. Faustino and Giovita annual Fair, February the 15th, 2020.**

Fig. 3 – **One of the 6 tents set up outside the hospital to accomodate patients waiting for an ordinary bed.**

struggling at the bottom of the national championship ranking, and to the contest between public and private healthcare institutions, which have long been similar in terms of quality of performance. On February 15th, the annual Saint Faustino and Giovita's Fair hosted about 230,000 people, packed like canned sardines in the centre streets, between stalls and artistic events (Fig. 2). On February 24, the General Manager of ASST Spedali Civili discloses to the press the first 4 SARS-Cov2 positive nasopharyngeal swabs, all harvested the day before. On February 29 the first patient died, and from that moment on, for 105 consecutive days, there were daily deaths – with up to about 80 deaths per day – for COVID19. Today, June 21th – the summer solstice – we cautiously celebrate the first day without deaths, grieving for 2714 people, 292% more than the expected mortality of the period (1, 2).

ASST Spedali Civili is a third-level academic hospital, affiliated with the University of Brescia, a university founded in the early 1980s and it has a total undergraduate enrolment of 15,000 students over 9 Departments, including 3 in medical area. With over 1500 beds, it is the largest hospital in Lombardy. From the sadly famous February 24, SARS-Cov2 cases rapidly rised, reaching 100 new hospitalizations per day in the hospital. On March 2, one of 2 General Surgery divisions was converted into "Covid Unit" (there will be 9 Covid Units at full capacity), and the hospitalized patients with SARS-Cov 2 infection reached more than 850 at the same time. The ICU places increased from 40 to 86. The external "Charlie" check point was set up, the Civil Protection assembled 6 large tents (Fig 3), hosting first 18, then 50, finally 70 beds to accommodate patients waiting up to 72

hours for receiving a hospital bed (the tents will host 1800 patients in 3 months). New hospitalizations and deaths followed one another at a fast pace, there were wards recording 10 deaths over 30 beds per day.

To us, general surgeons, it seemed that the earth was missing under the feet, like a chasm that opens more and more, day by day. First, hospital management forced us not to operate patients who might need intensive care, then they urged not to operate at all, owing to the lack of anesthesiologists and nurses, diverted to the Covid wards. We went from 15 to 2 operating rooms per week, and only really urgent cancer cases were considered for surgery. We got organized for more emergency interventions, by increasing the number of surgeons on call, because the hospital became a trauma surgery hub for Eastern Lombardy (4,000,000 inhabitants). Even in our wards, positive swabs were discovered in asymptomatic patients, but some of them subsequently developed pneumonia, they were not intubated because they had cancer and died in the postoperative period. Our morning briefing was a mixture of disbelief, pessimism, sensationalism, with more and more striking and restrictive rules, taken by the hospital management and by the regional health institutions. Outpatient clinics closed, digestive endoscopy closed, private activity closed, multidisciplinary groups closed, teaching closed. Scientific activity lost importance, and not to deal, from a scientific point of view, with Coronavirus, seemed to be insensitive, indifferent and cynical. Moreover, if you would like to publish on Coronavirus, you had to point out how everything had changed, everything had gotten worse (3, 4). Scientific journals, also top ranking, accepted papers without methodological peer-review (I remember with horror a survey among surgeons made via whatsapp that generated recommendations, accepted and published in a week). Even the Scientific Societies issued conflicting recommendations, especially on the topic of laparoscopy (5, 6). Our world had changed, nothing was like before.

I witnessed the first phase, the worst one, of this revolution, as a spectator/patient. On March 6th I had fever, swab immediately positive, on March 12th I was hospitalized for dyspnoea with moderate respiratory failure which responded well to oxygen in the mask, I took hydroxychloroquine and antiretrovirals (with side effects), and after 6 days I have been discharged with moderate respiratory and systemic residual symptoms. From home, I felt and followed more and more frightened, more and more depressed colleagues and friends, learning how to manage internal medicine cases, taking workshift in the emergency room, discharge room and extra-hospital triage. And I replied to many patients who asked to be treated for their non-Covid diseases by repeating like a mantra: "we can't do anything" and "we don't know, nobody knows". In short, a nightmare.

But the incredible thing, that in many moments you just can't even hope, is that everything passes. Everything. Week after week, the operating rooms have started to grow again, the Covid departments have been closed, the surgeons have started operating, with a process still in progress but that seems to be truly virtuous.

The trauma has been so severe at all levels that it also becomes a justification, real or presumed. Decrease in productivity, increase in morbi-mortality, work inertia of the categories not directly involved in the Covid patients care. It would be wrong not to admit that there have been differently effective responses in the different health systems of our country, and even in each hospital some problems have been tackled less adequately than others. But the extent of the event was such that mistakes are excused. The surge of respect and support for doctors and nurses by media and population has been sickly and delirious, taking on even ridiculous tones. The self-promotion of many doctors and groups of doctors, favoured by the social media, has diverted attention from the reality of multiple clinical and scientific failures. Not only. The trauma was so severe that the recovery is excessively slow. Today in Brescia, as in the rest of Italy, about 2 out of 100 swabs are positive, and the number can drop to 1 with a simple symptoms assessment. Therefore, all of our precautions in

managing patient access (to the operating room, to the ward, to the digestive endoscopy) are useless for 98 or 99 out of 100 patients, and harmful to many: for instance, I'm facing the difficulty of operating a young woman with achalasia who has lost 11 kg in 1 month, and an elderly woman with huge rectal prolapse that generates complete incontinence. Even in these choices, fear justifies everything.

In conclusion, what should we learn? Out of epidemiological considerations relating to the possibility of blocking the virus spread in the population, where should the surgeons improve the management of this and other emergencies? When I was hospitalized, after the first 72 hours in which I really desaturated without oxygen, I remained for another 3 days for simple observation, in much better clinical conditions than many patients waiting for a bed in ER or in the tents. Colleagues did not discharge me because it was not usual to discharge pneumonia until a complete resolution of the radiological picture. This was wrong. Just as it is wrong now not to quickly recede from the restrictive measures relating to the treatment of non-Covid pathology. The key word must be "elasticity", both on arrival and on the disappearance of a new wave of Covid19, or of another virus. Adaptation is the mechanism by which species survived and evolved, and major environmental changes were the engine that generated it. If we want – and we must do it – to see the SARS-Cov2 pandemic with constructive mind, let's consider it a great environmental change, and adapt!

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ARTIGO DE OPINIÃO

# BENEFÍCIOS DA TELEMEDICINA PARA OS DOENTES, OS SISTEMAS DE SAÚDE E A SOCIEDADE: USO DA TELEMEDICINA PARA O *FOLLOW-UP* DE DOENTES COM CANCRO

## BENEFITS OF TELEMEDICINE FOR PATIENTS, HEALTH SYSTEMS AND SOCIETY: THE USE OF TELEMEDICINE FOR CANCER PATIENTS FOLLOW-UP

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**RESUMO**

Actualmente, os sistemas de saúde enfrentam o enorme desafio de garantir o acesso equitativo a cuidados de saúde, melhorar a qualidade dos cuidados prestados e reduzir os custos associados a esses serviços. As estratégias e soluções para alcançar esse "triplo objetivo" e abrir o caminho para a melhoria do sistema de saúde como um todo, passam pela adopção de estratégias inovadoras que combinem a gestão da doença, o uso de sistemas de informação e tecnologias para melhorar o acesso a cuidados e resultados em saúde. A telemedicina quando totalmente integrada num sistema de saúde existente, é uma ferramenta poderosa que pode oferecer suporte a muitos doentes e contribuir para optimizar os recursos existentes. À medida que a ciência médica evolui com novas formas de responder às necessidades dos doentes, as organizações prestadoras de cuidados de saúde devem manter o doente no centro da sua missão ao implementar soluções de telemedicina, que melhorem as suas capacidades, alarguem o atendimento em tempo oportuno, conveniente, acessível e de elevada qualidade. Quando implementado cuidadosamente, um sistema de telemedicina flexível e escalável pode permitir um atendimento de qualidade ao longo de todo o espectro de cuidados, desde a triagem inicial e cuidados primários, até às especialidades hospitalares e atendimento no domicílio. A telemedicina orientada pela conveniência, facilidade e acessibilidade económica oferece aos sistemas de saúde um meio para que doentes e prestadores se comuniquem de forma mais eficiente, abrindo novas perspetivas no seguimento de doentes com cancro e outras doenças crónicas.

***Palavras-chave:*** *Telemedicina; Tumores; Acessibilidade aos Serviços de Saúde; Abordagem da doença; Seguimento de doentes.*

**ABSTRACT**

Currently, health systems face the enormous challenge of ensuring equitable access to health care, improving the quality of care and lowering the cost of care. Strategies and solutions to achieve this "triple aim" and open the way for the improvement of the health system as a whole, involve adopting innovative strategies that combine disease management, the use of information systems and technologies to improve access care and health outcomes. Telemedicine, when fully integrated into an existing health system, is a powerful tool that can support many patients and help to optimize existing resources. As medical science evolves with new ways responding to patient's needs, healthcare organizations must keep the patient at the center of their mission by implementing telemedicine solutions that improve their capabilities, extend timely, convenient, affordable and high quality of care. When implemented carefully, a flexible and scalable telemedicine system can enable quality across the entire spectrum of

care, from initial screening and primary health care, to hospital specialties and home care. Telemedicine guided by convenience, ease and affordability offers to the health systems a solution for patients and providers to communicate more efficiently, opening new perspectives in cancer patient follow-up of as well other chronic diseases.

***Keywords (MeSH):*** *Telemedicine; Neoplasms; Health Services Accessibility; Disease management; Follow-up studies.*

## INTRODUÇÃO

A pandemia COVID-19 obrigou à implementação de medidas de confinamento e limitações de mobilidade que conduziu ao recurso a tecnologias de comunicação como nunca antes visto, desde a educação on-line, o trabalho remoto em casa até à telemedicina. Neste novo cenário é legitimo questionar se a telemedicina é uma ameaça ao atendimento de doentes com cancro ou uma oportunidade que poderia revolucionar nossa prática clínica na próxima década. A telemedicina em oncologia não é uma novidade, sendo usada há vários anos especialmente como meio de comunicação para o atendimento de doentes em áreas remotas, com resultados satisfatórios. Este surto epidémico, com o bloqueio das cidades e o medo de contágio, tornou o uso da telemedicina amplamente aceite entre médicos e doentes e as suas vantagens antecipadas superaram claramente os receios existentes. Existe um consenso alargado relativamente à capacidade da telemedicina, ou seja, a prestação de serviços de saúde à distância, poder ajudar a melhorar a vida dos cidadãos, sejam eles doentes ou profissionais de saúde, contribuindo também para resolver alguns dos problemas dos sistemas de saúde. A telemedicina pode melhorar o acesso a cuidados de saúde especializados em zonas nas quais os especialistas disponíveis sejam insuficientes ou o acesso a cuidados de saúde seja difícil. A telemonitorização pode melhorar a qualidade de vida dos doentes crónicos e reduzir os dias de hospitalização. A telerradiologia, as teleconsultas e outros serviços podem ajudar a diminuir as listas de espera, a optimizar a utilização dos recursos e a conseguir maior produtividade. A Comissão Europeia define telemedicina como a prestação de serviços de saúde através da utilização das tecnologias da informação e das comunicações em situações em que os profissionais de saúde e o doente não se encontrem no mesmo local. A telemedicina compreende a transmissão segura de informações e dados médicos, necessários para a prevenção, diagnóstico, tratamento e seguimento dos doentes, por meio de texto, som, imagens ou outras vias[1]. A telemedicina abrange uma grande variedade de serviços, sendo os mais frequentemente referidos na literatura a telerradiologia, a telepatologia, a teledermatologia, a teleconsulta e a telemonitorização. Outros serviços possíveis são os centros de atendimento e de informação destinados aos doentes, as consultas à distância e as videoconferências entre profissionais de saúde.

## IMPLEMENTAÇÃO DE SERVIÇOS DE TELEMEDICINA EM DOENTES COM CANCRO

Os serviços de telemedicina podem usar uma variedade de tecnologias de telecomunicações para apoiar o atendimento clínico. Existem duas abordagens principais para os serviços de telemedicina: formato síncrono ou assíncrono. O doente e o médico podem conectar-se virtualmente de forma síncrona ou assíncrona. No primeiro caso, é usada tecnologia de vídeo totalmente interativa em tempo real. No segundo, são armazenados e transmitidos dados clínicos, como relatórios médicos, imagens e gravações de vídeo, para serem interpretados posteriormente. Os serviços de telemedicina, incluindo teleoncologia, podem usar um ou ambos os formatos, com ou sem

consultas pessoais com base nas necessidades clínicas. O exame físico pode ser realizado virtualmente, com exceção da palpação, e nesse caso os dados podem ser reportados pelo clínico local ao teleconsultor ou teleoncologista. Dadas as habilidades necessárias para a teleconsulta, a educação profissional sobre a prestação de serviços de telemedicina é essencial. A educação e as expectativas dos doentes em relação à telemedicina são fundamentais para a promoção de cuidados centrados no doente. Em 2008 na *eHealth High Level Conference Declaration* os representantes dos estados membros da Comissão Europeia reconheceram a urgência de uma maior difusão de serviços de telemedicina e de aplicações inovadoras das tecnologias da informação e das comunicações para a gestão de doenças crónicas, com o objectivo de apoiar os Estados-Membros na generalização de serviços de telemedicina, mediante a focalização em três categorias estratégicas de acções – a criação de confiança nos serviços de telemedicina, a clarificação jurídica e a resolução de aspectos técnicos e desenvolvimento.

## CONFIANÇA DOS PROFISSIONAIS DE SAÚDE E DOS DOENTES NAS SOLUÇÕES DE TELEMEDICINA

Os sistemas de saúde estão orientados para responder às necessidades dos doentes. O potencial da telemedicina só será alcançado se os doentes considerarem que esses serviços são capazes de satisfazer as suas necessidades clínicas. A aceitação por parte dos doentes depende, de modo determinante, da aceitação por parte dos profissionais de saúde que os tratam, dado o elevado grau de confiança que os primeiros depositam nos segundos. Um factor importante para conseguir a confiança e a adesão dos profissionais de saúde é a ampla divulgação da evidência da eficácia dos serviços de telemedicina, da segurança e facilidade de utilização desses serviços.

## DEMONSTRAÇÃO DA EFICÁCIA E RENTABILIDADE DA TELEMEDICINA

Existem evidências limitadas de eficácia e de custo-efetividade dos serviços de telemedicina em larga escala. A confiança e a aceitação pelas autoridades de saúde, profissionais e doentes ainda precisam de ser fortalecidas. Vários estudos demonstraram vantagens dos serviços de telemedicina para os doentes e para os sistemas de saúde. Há, porém, que aperfeiçoar as metodologias de avaliação da eficácia, porque pode ser difícil atribuir um valor tangível preciso aos factores que contribuem para os ganhos em eficiência e redução dos custos como: menos efeitos adversos; menos prescrições; menos absentismo laboral; ou melhor qualidade de vida dos doentes, que contribuem para aumentar a eficácia e reduzir custos. Por outro lado, é necessário ter em conta que pode haver uma redução das despesas de saúde num sector diverso daquele em que os investimentos foram inicialmente realizados. Para obter programas sustentados de telemedicina em larga escala, será essencial que o custo desses serviços seja reembolsado. No entanto, a disponibilidade das autoridades de saúde de reembolsar certos tipos desses serviços dependerá muito dos resultados dos estudos de eficácia e rentabilidade.

## PREOCUPAÇÕES COM A SEGURANÇA DO DOENTE

A rápida aceleração das capacidades de telemedicina pode ser útil para muitas instituições, no entanto, existem precauções críticas que devem ser tomadas para minimizar os riscos de segurança. Assim, as instituições devem estabelecer protocolos de escalonamento que determinem as condições em que um doente pode precisar de um atendimento presencial. Os protocolos de escalonamento devem ser identificados, desenvolvidos e aplicados no contexto de uma determinada prática e devem abranger a variedade de cenários possíveis, incluindo a necessidade de um nível mais alto de atendimento,

como uma consulta de urgência ou a necessidade de estudos de diagnóstico. Os prestadores do serviço devem ser incentivados a realizar o mapeamento das visitas dos doentes e determinar os agendamentos que podem ser convertidos em consultas de telemedicina e isso pode exigir comunicação adicional ao doente por enfermeiros ou assistentes clínicos para rever informações sobre o histórico clínico do doente, validar o motivo de sua visita, identificar a necessidade de serviços auxiliares e garantir que o doente entenda o que lhe é proposto. Devem ser desenvolvidos sistemas para que os médicos possam documentar os serviços de telemedicina prestados e integrá-los como parte do fluxo de trabalho regular. Devem ser incrementados os esforços para diminuir os riscos sociais, criando mais soluções para os doentes com menor nível de literacia. As instituições devem manter uma cultura de segurança, usando a criptografia de dados para proteger a privacidade dos doentes e implementando um plano de garantia de qualidade para as consultas de telemedicina, com análise e discussão dos casos com resultados positivos e negativos de segurança. Os profissionais devem estar envolvidos no desenvolvimento das diretrizes e protocolos operacionais, os quais devem ser atualizados regularmente. Em resumo, à medida que os profissionais e os doentes se forem familiarizando com os aspectos técnicos da telemedicina e os seus benefícios e limitações melhor compreendidos, a telemedicina, se implementada adequadamente, pode constituir uma abordagem inovadora com impacto para o futuro da prestação de cuidados de saúde seguros e de qualidade.

## ASPECTOS ÉTICOS

A maior difusão da telemedicina, suscita novas preocupações éticas, em especial no que diz respeito aos efeitos destas tecnologias na relação médico--doente. A implementação da telemedicina deve responder às necessidades dos utilizadores e aumentar e a confiança nesses serviços por parte dos doentes e dos profissionais de saúde, e ao mesmo tempo revelar-se vantajosa no que respeita à segurança e à qualidade dos cuidados prestados. As questões da privacidade e da segurança são também muito importantes para criar confiança nos sistemas de telemedicina. Na recolha e tratamento de dados pessoais, nomeadamente de dados relativos à saúde, é necessário garantir o respeito de direitos e liberdades fundamentais, como o direito à privacidade e o direito à proteção dos dados pessoais. Tal como qualquer outra transmissão de dados clínicos pessoais, a telemedicina pode comprometer o direito à proteção de dados. A questão da privacidade dos dados deve ser sempre avaliada na prestação de serviços de telemedicina.

## ASPECTOS JURÍDICOS

Embora a telemedicina possa ser uma opção interessante para muitas unidades de saúde, é conhecido o obstáculo que a falta de clareza jurídica coloca a uma maior difusão desses serviços. O objectivo principal da clarificação jurídica nesta área passa por assegurar que a telemedicina se desenvolva em benefício dos cuidados prestados aos doentes e que simultaneamente sejam garantidos a privacidade e os mais elevados padrões de segurança para os doentes. A falta de clareza jurídica – nomeadamente no que se refere ao licenciamento, acreditação e registo dos serviços e profissionais, assim como à responsabilidade, ao reembolso e à jurisdição – é um problema importante que se coloca neste tipo de serviços. A telemedicina é simultaneamente um serviço de saúde e um serviço da sociedade da informação, estando abrangida pelo Tratado CE (artigo 49) e pelo direito comunitário em vigor, nomeadamente a Directiva 2000/31/CE, designada por "Directiva sobre comércio eletrónico"[2].

## USO DA TELEMEDICINA PARA O *FOLLOW-UP* DE DOENTES COM CANCRO

Após a conclusão do tratamento primário do cancro, a maioria dos doentes entra num programa de acompanhamento estruturado, que envolve consultas presenciais regulares com médicos especialistas em oncologia. A frequência das consultas de acompanhamento varia de acordo com o tipo de tumor, o estadio e as normas de orientação clínica institucionais ou nacionais. Os cuidados de acompanhamento estão orientados à detecção da recidiva, à monitorização e tratamento dos efeitos secundários do tratamento e no suporte contínuo aos doentes e suas famílias. Os modelos actuais de *follow-up* de doentes com cancro provavelmente são insustentáveis devido, em primeiro lugar, ao envelhecimento da população e melhoria do tratamento, com o consequente aumento da prevalência de cancro, ano após ano[3]. Isso significa que os serviços são obrigados a seguirum número crescente de doentes e nem sempre com correspondente aumento de recursos. Em segundo lugar, o acesso a cuidados ulteriores pode ser problemático para certos grupos de doentes, especialmente aqueles que vivem em áreas remotas e distantes do hospital e com dificuldades de mobilidade ou de transporte. As modernas tecnologias oferecem capacidades e funcionalidades crescentes a doentes, profissionais e sistemas de saúde para a prestação de cuidados. A sociedade actual e a população de doentes com cancro está cada vez mais familiarizada com a tecnologia e consome informações e serviços de saúde em plataformas digitais, pelo que à medida que aumenta a prevalência do cancro é imperativo implementar e desenvolver novos modelos de cuidados com o recurso a novas tecnologias. No entanto, a implementação de novos modelos de *follow-up* de doentes com cancro obriga a avaliação criteriosa das evidências existentes sobre segurança clínica, aceitação dos doentes, relação custo-benefício e impacto na qualidade de vida dos serviços de telemedicina.

## ACEITAÇÃO E SATISFAÇÃO DOS DOENTES

Os dados sobre a satisfação ou aceitabilidade dos doentes foram reportados em vários estudos[4,5,6,7]. Beaver et al. referem que a maioria das mulheres com cancro da mama apresentavam níveis de satisfação equivalentes relativamente ao seguimento por meios tecnológicos em comparação aos cuidados usuais[4]. Kimman et al. constataram que o acompanhamento telefónico conduzido por uma enfermeira após tratamento curativo do cancro mama resultou em elevados índices de satisfação com o potencial adicional de reduzir o número de consultas[5]. O estudo de Hegel et al. reportou que 92% das mulheres norte-americanas com cancro mama que receberam durante 6 semanas acompanhamento telefónico na solução de problemas estavam altamente satisfeitas com a intervenção[7]. Não existe evidência de outros estudos que demonstrem uma redução da satisfação dos doentes associada às intervenções tecnológicas de *follow-up*.

## SEGURANÇA CLÍNICA

Apenas um estudo comparativo abordou de forma explicita a segurança clínica[4]. Foi realizado entre 374 mulheres com cancro mama, comparando o tempo para a detecção de recidiva, não revelando diferenças significativas observadas entre os grupos intervenção e controle.

## QUALIDADE DE VIDA

Um estudo norte-americano de monitorização de sintomas relacionados com a quimioterapia, demonstrou que os doentes que receberam monitorização de sintomas por telefone relataram sintomas mais graves do que aqueles que foram assistidos por um enfermeiro[8,9]. Um estudo australiano realizado em doentes com cancro colorretal que receberam acompanhamento telefónico

de uma enfermeira especialista, revelou índices de qualidade de vida mais elevados no grupo de intervenção aos seis meses [10]. Os participantes num estudo de intervenção sobre fadiga relataram uma diminuição nas pontuações em comparação com a linha de base na escala de fadiga, bem como uma redução da ansiedade e em vários índices funcionais do EORTC-C30[11]. No entanto, um estudo com 299 doentes com cancro de mama realizado na Holanda não reportou diferenças significativas na qualidade de vida entre o grupo de intervenção que recebeu acompanhamento telefónico e o grupo de controle que recebeu acompanhamento hospitalar[12]. Tendo em conta todos esses ensaios, não houve evidência de redução da qualidade de vida em nenhum dos grupos de intervenção.

## RESULTADOS ECONÓMICOS

A avaliação dos resultados económicos do uso de meios tecnológicos no follow-up de doentes com cancro é escasso. Num ensaio clínico randomizado que comparou o impacto económico do acompanhamento no centrado no hospital versus acompanhamento telefónico após o tratamento do cancro da mama, concluiu que o acompanhamento telefónico era mais dispendioso para os serviços de saúde, com consultas telefónicas mais longas que as consultas presenciais, mais pedidos de estudos de imagem ou reencaminhamentos adicionais. No entanto, o acompanhamento por telefone foi menos dispendioso para as doentes[13]. Por outro lado, um estudo prospectivo randomizado holandês que comparou quatro estratégias de acompanhamento após tratamento curativo do cancro de mama, concluíu que o acompanhamento hospitalar padrão associado um programa educacional resultou num maior ganho em termos de QALYs, em comparação com o acompanhamento telefónico, mas a um custo considerável, possivelmente devido ao elevado número de contactos efectuados no grupo de acompanhamento por telefone. Numa análise de subgrupos incluída neste estudo, o acompanhamento hospitalar associado a um programa educacional, mostraram ter a melhor relação custo-benefício em doentes ansiosos. A idade, o nível de escolaridade e a administração de quimioterapia não influenciaram a relação custo-benefício[14].

## RESUMO DA EVIDÊNCIA CIENTÍFICA

As evidências que suportam o papel da telemedicina no follow-up de doentes com cancro são consistentes e demonstram que a telemedicina contribui para a continuidade de cuidados, diminui o custo do tratamento e melhora os resultados clínicos globais. Os dados disponíveis sugerem que o uso da telemedicina para seguimento de doentes com cancro é aceitável para os doentes e clinicamente seguro. No entanto, actualmente não existe evidência suficiente para afirmar definitivamente que o acompanhamento remoto do dos doentes com cancro usando a tecnologia é ou não rentável, uma vez que a maioria das evidências existentes se referem a modelos alternativos de acompanhamento usando apenas o contacto telefónico. Os resultados de que dispomos são importantes para investigação futura, uma vez que no momento em que nos encontramos, com o envelhecimento progressivo da população e o aumento do número de sobreviventes de cancro, é imperativo encontrar alternativas aceitáveis, seguras e economicamente viáveis para os atuais modelos de prestação de cuidados de saúde. As evidências existentes sugerem que o *follow-up* de doentes com cancro pode ser realizado com recurso á telemedicina sem reduzir a satisfação dos doentes, comprometer a segurança, prejudicar a qualidade de vida ou aumentar o sofrimento psicológico.

## CONCLUSÃO

Desde há vários anos que são usadas no IPO Porto várias formas de telemedicina em doentes com

cancro, desde a teleradiologia, a telemonitorização de doentes sob quimioterapia oral, a telemonitorização dos doentes submetidos a cirurgia incluídos em protocolo da recuperação acelerada e as videoconferências multidisciplinares com outros hospitais. A pandemia COVID-19 e as incertezas relativas à duração do surto epidémico obrigou à implementação de um plano de contingência associado a um conjunto medidas e soluções orientadas pelo dever ético de garantia acesso, utilização criteriosa de recursos e continuidade na prestação de cuidados de saúde. Uma destas medidas consistiu na implementação da telemedicina para realização de consultas não presenciais para doentes em *follow-up*. Com a experiência dos últimos 3 meses, apesar de não dispormos de métricas relativas à segurança e qualidade de vida, dispomos de dados que suportam uma elevada aceitação e satisfação dos doentes e dos profissionais com a telemedicina como uma alternativa ou complemento aos modelos tradicionais existentes, capaz de proporcionar um acompanhamento estruturado, seguro e eficaz dos doentes com cancro. Os ganhos potenciais oferecidos pela tecnologia digital em termos de conveniência do doente e redução do uso de recursos limitados do hospital, torna imperativa a implementação e a investigação de modelos inovadores de acompanhamento dos doentes com cancro. O uso destas tecnologias pode libertar mais tempo para o médico, que por sua vez pode concentrar-se em actividades de maior valor em saúde, permitindo uma melhor coordenação do atendimento dos doentes, com economia de tempo, custos mais baixos, acesso facilitado e cuidados individualizados.

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PERSPECTIVAS

# CIRCULATING TUMOUR CELLS: A PORTUGUESE CONTRIBUTION TOWARDS PRECISION MEDICINE

## CÉLULAS TUMORAIS CIRCULANTES: CONTRIBUIÇÃO PORTUGUESA PARA A MEDICINA DE PRECISÃO

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**ABSTRACT**

In the context of cancer, liquid biopsy refers to the capture and subsequent analysis of tumour material, such as circulating tumour cells (CTCs), circulating tumour nucleic acids and tumour-derived extracellular vesicles, present in the blood of patients with cancer, or even in other body fluids. CTCs are shed from primary tumours or metastatic sites and have a short half-life in circulation, therefore providing information about the biology of cancer in real time and holding great potential as a biomarker for cancer diagnosis, management, and prognosis. As a result, several technologies have been developed over the years in order to efficiently capture these cells with the ultimate goal of revolutionizing cancer assessment. A great focus is deserved on microfluidic-based approaches for CTC isolation, as they provide unprecedented sensitivity and purity, while keeping low cost. In this article, we discuss the huge impact that CTCs could have in oncology and ultimately in precision medicine regarding its greatest advantages against other circulating biomarkers, but we also consider its main limitations and current challenges to be implemented into the clinic.

***Keywords:*** *Circulating tumour cells, CTCs, Cancer, Metastasis, Liquid Biopsy.*

**RESUMO**

No contexto do cancro, a biopsia líquida é uma metodologia que se baseia na captura e análise de material de origem tumoral, tal como células tumorais circulantes (CTCs), ácidos nucleicos e vesiculas extracelulares, que se encontram em circulação no sangue de doentes com cancro, ou até mesmo noutros fluídos corporais. As CTCs são libertadas pelo tumor ou por lesões metastáticas, permitindo a obtenção de informação em tempo real sobre a biologia do cancro, conferindo-lhes um grande potencial para se tornarem biomarcadores úteis para o diagnóstico, gestão e prognóstico do cancro. Nos últimos anos, várias metodologias têm sido desenvolvidas com vista à captura eficiente destas células. Em particular as metodologias baseadas em microfluídica têm merecido especial atenção, uma vez que permitem obter elevada sensibilidade e pureza a baixo custo. Neste artigo, discutimos o grande impacto que as CTCs podem ter, não apenas na oncologia clínica, mas em última instância na medicina personalizada salientando as vantagens que as destacam comparativamente a outros biomarcadores circulantes. Temos, ainda, em consideração as suas principais limitações e atuais desafios à sua implementação na clínica.

***Palavras-chave:*** *Células tumorais circulantes, CTCs, Cancro, Metástases Biopsia Líquida.*

Over the past years, liquid biopsy has emerged as a promising diagnostic and prognostic tool in cancer, since it allows a better insight into tumour heterogeneity through a non-invasive type of sampling. This biopsy refers mainly to the extraction of a peripheral blood sample from a cancer patient and the subsequent isolation of a diversity of tumour-associated components, such as circulating tumour cells (CTCs), circulating nucleic acids and tumour-derived extracellular vesicles that are released from the primary or metastatic tumours into the bloodstream[1]. There are several sources of nucleic acids that can be found in cancer patients' blood including circulating cell-free DNA (cfDNA) and cell-free RNA (cfRNA), despite not being necessarily directly released from the tumour, a subset of these represent circulating tumour DNA (ctDNA), which is tumour-derived fragmented DNA.

CTCs, presented in the blood as cells or clusters, are viable non-hematological cells with malignant features and short life-span that are ultimately responsible of the metastatic process. Metastasis is however an extremely inefficient process and most CTCs die once in the bloodstream by suffering apoptosis, due to the action of the innate immune system, shear forces or even oxidative stress. However, those that survive are the most interesting ones due to their ability to escape the immune response, resist the harsh conditions, move to a distant location, undergo mesenchymal-to-epithelial transition (MET) and adapt, colonize and survive in the new tissue-specific microenvironment, where they finally grow to form metastasis[1].

Despite the CTCs and their role has been known since the nineteenth century, to date the capture of CTCs remains technically challenging due to the very low concentration of these tumour cells in the background of millions of blood cells. Therefore, extremely sensitive, and specific analytic methods are required first for the isolation/capture, and then for the enumeration or characterization of these cells[2]. Different approaches for CTC isolation have been reported and they can be mainly classified according to physical or biological properties of the CTCs[3]. CTC isolation methods based on physical properties are label-free and rely either on cell size, density, electric charge, or deformability to allow efficient separation from blood cells. On the other hand, technologies based on biological properties include mainly recognition of proteins expressed in the cell-surface and involve immunologic procedures to enrich the cellular fraction of the sample[4].

Up until now, the CellSearch® system is the most widely used technology for CTC isolation and enumeration and the only method approved by the FDA in the context of metastatic breast, prostate and colorectal cancer. It operates through immunomagnetic antibodies against the protein EpCAM, which is expressed in the membrane of epithelial CTCs, but not in blood cells. Then a cross characterization is performed by staining the captured cells to demonstrate the presence of the nucleus and by immunofluorescence analysis with antibodies against cytokeratin (CK) and CD45. Hence, in order to be considered a CTC, a cell must have a nucleus, possess an intact membrane, be positive for CK – proving its epithelial origin-,and negative for CD45 to be excluded as a blood cell[5]. Nonetheless, there are some limitations regarding the CellSearch® system that are related to the EpCAM dependent-enrichment, since this protein is downregulated in CTCs during epithelial to mesenchymal transition, the process that enables cells with increased plasticity and capacity for migration and invasion[5]. In addition, not all cancers have an epithelial origin and, in those, EpCAM is not expressed, therefore other cell phenotypes will not be detected, including mesenchymal and EMT CTCs. This limitation in combination with necessary sample pre-processing steps, accounts for significant cell loses, which results in low CTC capture efficiency using this system[6].

In order to improve CTC capture and identification, several techniques have been developed in the past years. Still, microfluidic-based approaches lead the technological advancements in the field, allowing the separation of CTCs from other blood components mainly based on their physicochemical

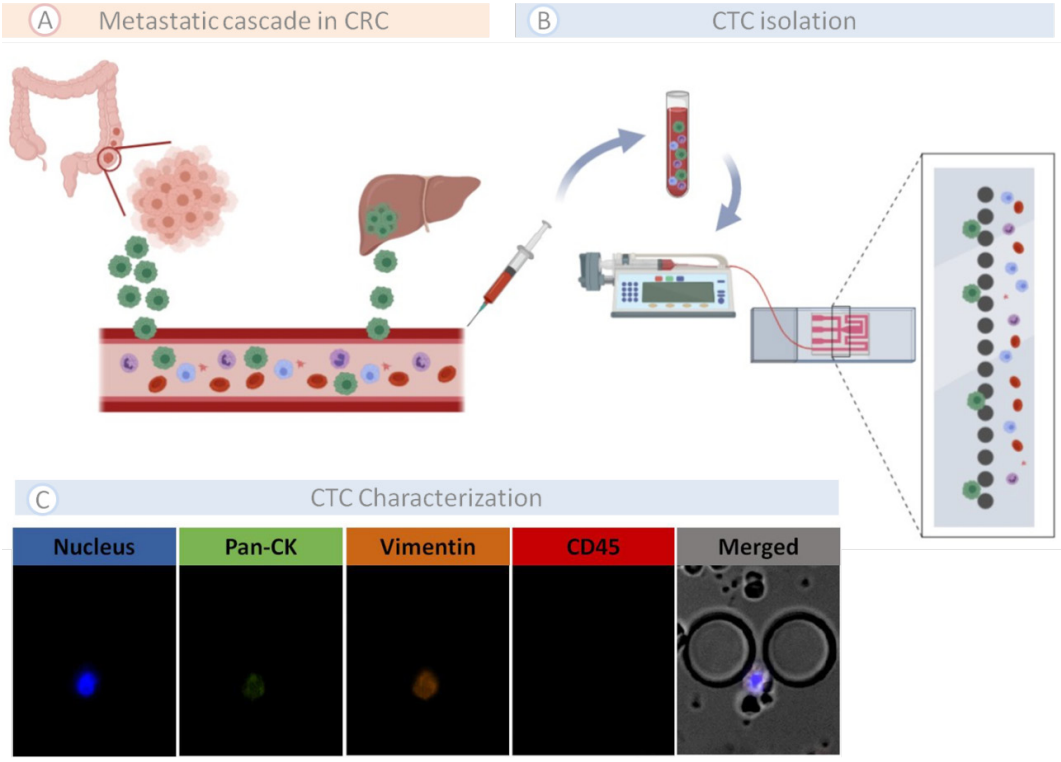


Figure 1 – ***A) Metastatic cascade in colorectal cancer. Cancer cells from the primary tumour travel though the bloodstream to distant organs. Circulating tumour cells (CTCs) must be able to evade the innate immune response, adapt to the microenvironment and initiate proliferation at the secondary site in order to develop a metastatic lesion. Metastatic tumours can also shed CTCs into circulation. B) Peripheral blood is an ideal source for the detection of CTCs. Size-based microfluidic CTC isolation has recently demonstrating its advantages compared to standard methodologies and has the potential to lead new developments to demonstrate the clinical utility of CTCs. C) Immunocytochemistry protocols can be optimised to discriminate the cells trapped inside the microfluidic device. CTCs are classified as intact nucleated cells (DAPI-blue) that express CK (green) and do not express CD45 (red).*** Figures were created with BioRender.com

characteristics, often without the need of prior sample processing, and enabling either *in situ* analysis or recovery of an enriched cell fraction for downstream molecular studies. Moreover, microfluidics provides many other significant advantages, enabling a cost-effective, simple, and automated operation, while reducing sample and reagent demands to carry out highly sensitive cell isolation as well as allowing miniaturization and portability. Many microfluidic devices recently developed are currently undergoing validation with promising results, and actually some of them have already entered clinical trials.

The study of CTCs in Portugal is very recent. From the over 22,000 original research articles published on the topic worldwide since the year 2000 (according to the Web of Science), only 11 had authors from Portuguese institutions. Of those, only 9 indeed studied CTCs from patients, and the rest where proof-of-concept studies using animal models or cell lines. From these 9 articles, 4 focused in molecular analysis of the genetic material extracted from the white fraction and another one used standard flow cytometry to study CK+ cells in blood with very poor efficiency[7]. The remaining 4 publications are from the last 4 years and coming from our groups, and demonstrate novel techniques for the isolation and analysis of circulating tumour cells.

These recent efforts in Portugal were devoted to the development of a microfluidic device that allows efficient isolation of viable CTCs based on their size and deformability from an unprocessed blood sample, and posterior identification *in situ*, using

antibodies against CK and CD45[8]. Since the isolation is independent of surface markers, this methodology allows the incorporation of other biomarkers to identify CTC subpopulations, for example the ones undergoing EMT or expressing other phenotypes, such as altered glycosylation. Until know, using this technology, the authors were already able to identify CTCs in samples from bladder, colorectal, gastric, pancreatic, esophageal and head and neck cancer patients (Figure 1)[8,9,10]. The technology was also compared against the gold standard in a head-to-head study, demonstrating superior performance of the microfluidic system in a small cohort of metastatic colorectal cancer patients, detecting more CTCs and consequently predicting recurrence 6-months to 1-year earlier[8].

Several studies have already demonstrated the prognostic value of CTCs, as their presence and number has been correlated with disease stage, reduced progression-free survival (PFS) and overall survival (OS). A number of studies that enumerated CTCs at different time points during treatment in distinct types of cancers, showed that an increase in CTC counts predicted disease progression, while a reduction correlated with improved PFS and OS[11,12].

The potential of CTCs is, however, far beyond prognostic. CTCs have been found to be an efficient biomarker in (i) patient screening and stratification, (ii) guiding treatment decisions, (iii) predicting relapse, and (iv) predicting therapy resistance in individual patients based on their particular molecular signature much earlier than conventional technologies[10]. To enhance the clinical value of CTCs as biomarkers to identify therapeutic targets, downstream analysis of the CTCs may be required. Molecular and phenotypic characterization of CTCs will allow an earlier and more accurate interpretation of the patients' response to therapy, by providing a non-invasive approach for tumour profiling in real time. This procedure can be repeated regularly during treatment to monitor the acquisition of new genetic alterations in response to the pressure of treatment[8]. In contrast with ctDNA that originates from necrotic and apoptotic cells, CTCs provide mutational information from live resistant cells, and also allow multi-omics analysis (transcriptomics, proteomics, metabolomics, etc) and functional studies. Furthermore, single-cell analysis of CTCs also opens the possibility to find resistant clones that could be responsible of metastasis-initiation. The analysis of these clones would be an enormous step towards understanding the metastatic process and, at the same time, open a new opportunity for clinicians to use alternative treatment strategies that might prevent the expansion of resistant clones. Finally, and most importantly, designing personalised therapeutic strategies for each patient, based on CTC analysis, would minimise the exposure to inefficient therapies and their potentially harmful side effects, increasing patient compliance and quality of life.

In parallel, since CTCs are shed from different heterogeneous sites within the tumour, and/or from different metastases, their analysis provides real time information about the biology of the cancer. In this sense, the development of personalised CTC-derived 3D models holds great promise for the development and screening of drugs[11,14]. To be able to perform functional studies with the CTCs upon their isolation, it is imperative for the cells to be viable after the recovery process. In this line, several studies have been reported to successfully expand CTCs in culture, establishing cell lines and also implanting xenografts in animal models. This field opens new perspectives for future *in vitro* and *in vivo* drug testing studies, including the supervision of the dynamic patterns of a tumour's drug susceptibility. New therapeutic targets could also be screened in a patient-derived model, revealing the molecular basis of drug response or resistance. With the fast development of this field, in the near future, CTCs could be used as pharmacological markers allowing physicians to design rational combinational therapies, select optimal doses, schedule antineoplastic drug administration, and ultimately predict treatment outcomes[14,15,16].

Besides the validity of CTCs for the real time evaluation of metastatic lesions and the potential

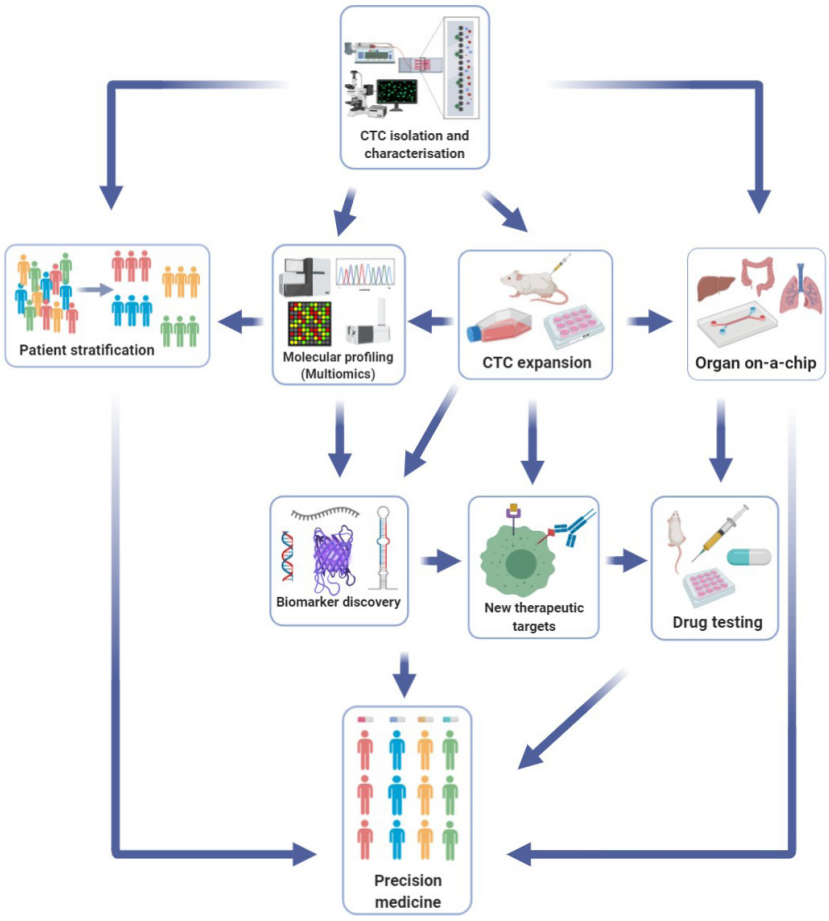


Figure 2 – ***CTC analysis is a multimodal diagnostic tool that enables precision medicine in cancer. This flow chart shows the combination of diagnostic tools and therapeutic strategies that derive from CTC isolation and characterisation and that will ultimately enable the realisation of precision medicine.***
Figures were created with BioRender.com

clinical utility as a monitoring tool during systemic therapy, liquid biopsy also shows potential in an early setting, as CTCs have been reported to be in circulation during primary disease[17]. In this setting, the analysis of CTCs could provide primary diagnosis in tumours where tissue biopsy is difficult, unfeasible or inaccessible[15]. Still, to undercover the full potential of CTCs and e include them into clinical routine, further technological advances are still required, important to achieve low-cost and high-throughput CTC isolation and characterisation systems that present minimal inter-user and inter-laboratory variability[18].

Real-time liquid biopsies have the potential to become, in the near future, an important landmark of precision medicine. The well-known cancer heterogeneity means that each patient is unique, and that two patients with the same condition, sharing the same tumour localization, histopathological classification and stage, can still present different outcomes and response to treatment. This is due to the fact that each cancer cell has different characteristics in terms of metabolism, mutational burden, gene expression and regulation and also protein translation[16]. Since each patient is different, the choice of treatment should be individual, with the ultimate aim of achieving an effective therapeutic outcome through the application of precision medicine (Figure 2).

Although there is extensive literature showing the prognostic value of CTCs and their clinical validity, their clinical utility has not yet been demonstrated and, consequently, its assessment is not yet recommended in cancer guidelines neither for diagnosis, nor to influence treatment decisions. There are many reasons for this lack of consensus, among them a lack of a standardization on sampling

frequency[11]. Generally, single or infrequent CTC sampling points are applied always assuming that changes in CTC counts are gradual, according to the success of the therapy applied, however CTC kinetics are not yet fully understood[11]. In order to elevate the knowledge in this area we are preparing several prospective studies in various cancer models, such as digestive tract (colorectal, gastric, esophageal and pancreatic cancer) and sarcomas.

Notwithstanding the limitations currently being addressed, CTCs appear as one of the most promising and versatile biomarkers in translational oncology. Once the scientific community is able to overcome the technical limitations associated to the CTC field, CTC-based liquid biopsy may emerge as an alternative to tissue biopsy with the ultimate goal to be incorporated into disease management strategies. In the meantime, perhaps we should benefit from liquid biopsy as a complementary approach to be used in conjunction with tissue biopsy, radiologic imaging, serum tumour markers, and clinical assessment, for real-time monitoring of disease status and therapeutic efficacy[11].

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# CLINICOPATHOLOGICAL CHARACTERISTICS OF BREAST CANCERS DIAGNOSED IN PARTICIPANTS, NON-PARTICIPANTS AND NOT INVITED TO THE BREAST CANCER SCREENING PROGRAMME IN NORTHERN PORTUGAL (2003-2008): PART ONE – EVALUATION.

## CARACTERÍSTICAS CLINICOPATOLÓGICAS DOS CANCROS DA MAMA DIAGNOSTICADOS EM PARTICIPANTES, NÃO PARTICIPANTES E NÃO CONVIDADOS AO PROGRAMA DE RASTREIO DE CANCRO DA MAMA NO NORTE DE PORTUGAL EM (2003-2008): PARTE UM – AVALIAÇÃO

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**ABSTRACT**

The aim of this study was to evaluate the clinical and pathological characteristics of the invasive breast cancers diagnosed in women participant in the beginning of breast cancer screening programme, compared to cancers detected in non-participants and in not invited women. Data was retrieved from the population-based North Region Cancer Registry and from the organized population-based Breast Cancer Screening Programme (BCSP) of the north region of Portugal, and records were matched to select the three groups for comparison. In 125 screening participants, 75.8% of invasive breast cancers were ≤ 20 mm, 67.7% had no axillary lymph nodes metastasis and 58.1% were stage I. These characteristics were significantly more favourable than those found in breast cancers detected in non-participants (57 women) or not invited (314 women). After multivariable analysis, size remained the only distinguishing characteristic of breast cancers detected within the screening programme compared to the other two studied groups. Breast cancers detected in screening participants were significantly smaller, which is consistent with findings by other authors. The more favourable prognostic characteristics of the breast cancers detected in a population exposed to screening (including interval cancers) indicate a possible mortality reduction in the future.

***Keywords:*** *Breast cancer; organized screening; non-participants; mammography.*

**RESUMO**

O objetivo deste estudo foi avaliar as características clínicas e patológicas dos cancros invasivos da mama, diagnosticados em mulheres participantes no programa de rastreio do cancro da mama, em comparação com os cancros detetados em não participantes e em mulheres não convidadas. Os dados foram obtidos do Registo Oncológico Regional do Norte, registo de base populacional, e do Programa de Rastreio de Cancro da Mama (PRCM), organizado, de base populacional da região norte de Portugal; foi avaliada a correspondência entre os dados para selecionar os três grupos para comparação. Em 125 participantes de rastreio, 75.8% dos cancros da mama invasivos eram ≤ 20 mm, 67.7% não tinham metástases nos gânglios linfáticos axilares e 58.1% eram estadio I. Estas características eram significativamente mais favoráveis do que as encontradas em cancros da mama detetados em não participantes (57 mulheres) ou não convidadas (314 mulheres). Após análise multivariável, o tamanho permaneceu a única característica distintiva dos cancros da mama detetados no âmbito do programa de rastreio em comparação com os outros dois grupos em estudo. Os cancros da mama detetados nas participantes do rastreio foram significativamente menores, o que é consistente com achados de outros autores. As características prognósticas mais favoráveis dos cancros da mama detetados numa população exposta ao rastreio (incluindo cancros de intervalo) indicam uma possível redução da mortalidade no futuro.

***Palavras-chave:*** *Cancro da mama; Rastreio organizada; Não participantes; Mamografia.*

## INTRODUCTION

High-quality population-based breast cancer screening programmes, with periodic mammographic examination of asymptomatic women became an important tool in cancer control (Dijck & Schouten, 2000; Lynge *et al.*, 2012). For logistic reasons the implementation of a new population-based screening programme in a certain country (or region) can take several years till it is fully implemented in all the geographical area considered; for that reason, during a certain time period, it happens that very similar neighbouring populations are being covered or not by the programme, creating an opportunity to compare likely outcomes between populations (Lynge *et al.*, 2012).

Comparisons of characteristics of the cancers diagnosed in women invited or not to an organized screening programme, and the analysis of differences between screened-detected and symptomatic breast cancers, have been used as a further approach in the evaluation of screening programmes (Shen *et al.*, 2005; Baré *et al.*, 2006; Bucchi *et al.*, 2008; Allgood *et al.*, 2011; Hofvind *et al.*, 2012; Nagtegaal & Duffy, 2013).

The organized population-based Breast Cancer Screening Programme (BCSP) implemented in the Northern Region of Portugal, conducted by the north branch of the Portuguese Cancer League (*Liga Portuguesa Contra o Cancro* – LPCC) started in 1999 in one municipality and gradually expanded its coverage in the north region (5 districts and 68 municipalities). In the period 2008/2009, a participation rate of 74.5% and coverage rate by invitation was 99.6% were achieved (Bento *et al.*, 2015). BCSP was implemented in the district of Bragança between 2003 and 2005 when full coverage was reached; in 2005, the estimated number of women aged 50-69 years living in the district was 19 554, representing 5.3% of the estimated 372 015 women of the same age living in the whole northern region. Bragança and Vila Real are neighbouring districts, with the same socioeconomical and cultural features and very close background breast cancer incidence (RORENO, 2002). In Vila Real the organized screening programme was only launched in 2009; in 2005, the estimated number of women aged 50-69 years living in this district was 27 644, representing 7.4% of the women of the same age group in the northern region.

We aimed at further contributing to the assessment of BCSP. For that purpose, the specific objective of this study was to compare the characteristics of the invasive breast cancers detected in populations with different screening exposure/participation status in our organized screening programme, regarding the beginning of the screening programme (part one).

## METHODS

Briefly, the methods implemented at the BCSP were the following: every two years women aged between 45 and 69 years were sent a letter with an invitation for a two-view mammography examination at one of the mobile or fixed units. A blind-double reading was systematically performed at a dedicated centre by trained radiologists with a final reading by a third independent and experienced radiologist, in case of discrepancy. Since the beginning of the screening programme it has been operating in accordance with the European Guidelines (Perry *et al.*, 2006) and preliminary results have been published (Giordano *et al.*, 2012). A specific database with individual records for the screening procedures and results was created in 1999 (BCSP database).

Invasive breast cancers diagnosed in women resident in the northern region of Portugal have been registered since 1988, at the population-based North Region Cancer Registry (*Registo Oncológico Regional do Norte* – RORENO) which has high completeness (Castro *et al.*, 2012).

Data was retrieved from RORENO using the following criteria: invasive breast cancers diagnosed between 2003 and 2008, in women aged 50-69 years at diagnosis (to be in accordance with age group considered in the European Guidelines) (Perry *et al.*, 2006) and resident in the districts of Vila Real and Bragança. Then, information on the screening history of breast cancers in women resident in Bragança was retrieved from the BCSP database. Variables as name, date of birth and national health number were used for matching. Similar to the "screening exposure" (Baré *et al.*, 2006) and "participation" (Hofvind *et al.*, 2012) status classifications used by other authors, the above described information was used to select three groups for comparison:

- women invited and participating in the screening, including screen-detected cancers and interval cancers (residents in Bragança) named *participants* in this analysis;
- women invited but not participating in screening, including women who never attended organized screening procedures, and those whose last participation had been more than 2 years before (residents in Bragança), named *non-participants;*
- women not invited to screening, which includes two subgroups: those resident in Vila Real district, who were not invited to screening in the study period, and women resident in Bragança district with breast cancer diagnosed prior to an invitation to participate in the screening programme, named *not invited*.

Data collected from the BCSP and RORENO databases included the patient date of birth, date and round of last mammography, outcome of screening, screening exposure/participation status (participants, non-participants, not invited), municipality of residence, date of diagnosis of breast cancer, age at diagnosis, tumour size in mm (with further division in 3 groups, according to the cut-offs of the European Guidelines) (Perry *et al.*, 2006), histological type using the International Classification of Diseases for Oncology-3$^{rd}$ edition (8500, 8521 coded as ductal; 8520, 8522, 8524 coded as lobular; 8211, 8480, 8510, 8530, 8540 coded as other), histological grade according to Nottingham Grading System (Elston & Ellis, 1991), lymph node status, tumour stage (TNM classification – AJCC (Greene *et al.*, 2002)), first treatment (mastectomy, breast conserving surgery, chemotherapy). In cases with upfront chemotherapy, a clinical T and N were assigned. Information on biomarkers as oestrogen (ER) and progesterone (PR) receptors status, and detection of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2) were registered according to the pathology reports.

Breast cancers detected in women participating in screening, in non-participants and in women not invited to screening were compared for each of the aforementioned variables. Comparisons were made pairwise. Proportions were compared using the Pearson $\chi^2$ test or Fisher's exact test when $\chi^2$ test

was not applicable, and one-way analysis of variance was used to compare the means of the continuous variables.

Unconditional multivariable logistic regression was used to assess the association between screening exposure/participation status and clinicopathological characteristics of breast cancer adjusted for possible confounder factors. Two models were tested for comparison of cancers detected in participants *versus* non-participants (including tumour size, lymph node status, grading, as covariates) and screening participants *versus* not invited (including tumour size, lymph node status, ER and PR expression, as covariates). Tumour size in the multivariable analysis was considered as ≤20 mm or > 20 mm. Since none of the screening participants had breast cancer with distant metastasis at diagnosis, this variable was not included in the multivariable models. HER2 was not used in this analysis, due to the small number of cases with this information. Differences were considered statistically significant for $P < 0.05$.

## RESULTS

Between 2003 and 2008, 34476 exams were performed, with 125 breast cancer cases being detected in women participating in the programme (113 screen-detected and 12 interval cancers) and 57 breast cancers being diagnosed in non-participants, including 7 women with more than 2 years since last mammogram. In the same period, 314 cancers were detected in women not invited to screening, 278 were residents in Vila Real and 36 in Bragança.

The mean age of all (n= 496) selected women with breast cancer was 59.7±5.7 years, and there was no significant difference ($P = 0.56$) between the three groups. In table 1 are shown the main clinical and pathological characteristics of the three groups.

The predominant histological type was ductal and the proportions were very similar between groups.

In the group of screening participants, the proportion of cancers with maximum size ≤10 mm was 30.1%, < 15 mm was 52.1% and 75.8% were ≤ 20 mm. Compared to non-participants or not invited, screening participants had a significantly higher proportion of smaller breast tumours ($P < 0.001$ for the three cut-offs used).

When cancer dimensions were compared between non-participants and not invited groups, the proportion of breast cancers with a maximum dimension greater than 20 mm was significantly higher in the first group (66.7% compared to 49.5%, $P = 0.02$); when size cut-off values used were of 10 and 15 mm, no significant differences were observed. For all the other variables, there were no significant differences between these two groups (non-participants and not invited).

Cancers detected in participants were found to be better differentiated than those detected in non-participants ($P = 0.002$); compared to not invited group, participants had lower grade tumours, though significance ($P = 0.06$) was slightly above the classical significance level.

The tumours in screening participants had less frequently lymph node metastasis than non-participants or not invited groups ($P = 0.005$ and $P = 0.006$, respectively). None of the cancers in participants had distant metastasis at diagnosis and it was significantly different from the 4.2% of the cancers with distant metastasis detected among the not invited ($P = 0.02$). In non-participants, 1.9% (one case) had distant metastasis at diagnosis and it was not significantly different from the group of participants.

Cancers in participants were more frequently found in an earlier stage than in each of the other two groups, with 58.1% of the cancers detected in stage I among participants ($P < 0.001$ for both comparisons, table 1). At diagnosis, 22.2% and 37.5% of the breast cancers diagnosed in non-participants and in the not invited group, respectively, were classified as stage I.

Cancers in participants showed significantly higher proportion of ER and PR positivity than cancers in the not invited group ($P = 0.036$ and $P = 0.009$, respectively) but a similar proportion when compared with breast cancers of non-participants. Although in

Table 1 – **Distribution of clinicopathological characteristics of invasive breast cancers diagnosed in women participant, in non-participant and not invited to the organized population-based Breast Cancer Screening Programme in 2003-2008.**

| Clinicopathological characteristics | Exposure/participation status | | | Significance level | | |
|---|---|---|---|---|---|---|
| Variable value | Participants (P) n = 125 (%*) | Non-participants (NP) n = 57 (%*) | Not invited (NI) n = 314 (%*) | P value P/NP | P value P/NI | P value NP/NI |
| Histology | | | | | | |
| Ductal | 109 (87.2) | 49 (86.0) | 271 (86.3) | 0.27 | 0.57 | 0.63 |
| Lobular | 13 (10.4) | 4 (7.0) | 29 (9.2) | | | |
| Other | 3 (2.4) | 4 (7.0) | 14 (4.5) | | | |
| Tumour size | | | | | | |
| ↖10 mm | 37 (30.1) | 3 (5.6) | 30 (11.2) | ←0.001 | ←0.001 | 0.22 |
| →10 | 86 (69.9) | 51 (94.4) | 239 (88.8) | | | |
| Missing | 2 | 3 | 45 | | | |
| Tumour size | | | | | | |
| ←15 mm | 63 (52.1) | 8 (19.0) | 55 (24.2) | ←0.001 | ←0.001 | 0.47 |
| ↗15 mm | 58 (47.9) | 34 (81.0) | 172 (75.8) | | | |
| Missing | 4 | 3 | 87 | | | |
| Tumour size | | | | | | |
| ↖20 mm | 94 (75.8) | 18 (33.3) | 142 (50.5) | ←0.001 | ←0.001 | 0.02 |
| →20 mm | 30 (24.2) | 36 (66.7) | 139 (49.5) | | | |
| Missing | 1 | 3 | 33 | | | |
| Tumour grade | | | | | | |
| Grade 1 | 27 (23.1) | 8 (16.3) | 48 (19.4) | 0.002 | 0.06 | 0.15 |
| Grade 2 | 75 (64.1) | 23 (46.9) | 141 (57.1) | | | |
| Grade 3 | 15 (12.8) | 18 (36.7) | 58 (23.5) | | | |
| Missing | 8 | 8 | 67 | | | |
| Lymph nodes | | | | | | |
| negative | 84 (67.7) | 24 (45.3) | 143 (53.0) | 0.005 | 0.006 | 0.31 |
| positive | 40 (32.3) | 29 (54.7) | 127 (47.0) | | | |
| Missing | 1 | 4 | 44 | | | |
| Distant metastasis | | | | | | |
| Negative | 124 (100) | 53 (98.1) | 271 (95.8) | 0.30 | 0.02 | 0.40 |
| Positive | 0 (0) | 1 (1.9) | 12 (4.2) | | | |
| Missing | 1 | 3 | 31 | | | |
| Stage | | | | | | |
| I | 72 (58.1) | 12 (22.2) | 106 (37.5) | ←0.001 | ←0.001 | 0.11 |
| II | 40 (32.3) | 23 (42.6) | 94 (33.2) | | | |
| III | 12 (9.7) | 18 (33.3) | 71 (25.1) | | | |
| IV | 0 | 1 (1.9) | 12 (4.2) | | | |
| Missing | 1 | 3 | 31 | | | |
| ER status | | | | | | |
| Positive | 108 (87.8) | 43 (84.3) | 206 (78.9) | 0.54 | 0.036 | 0.38 |
| Negative | 15 (12.2) | 8 (15.7) | 55 (21.1) | | | |
| Missing | 2 | 6 | 53 | | | |
| PR status | | | | | | |
| Positive | 96 (78.0) | 38 (74.5) | 167 (64.7) | 0.61 | 0.009 | 0.18 |
| Negative | 27 (22.0) | 12 (25.5) | 91 (35.3) | | | |
| Missing | 2 | 6 | 56 | | | |
| HER2 status | | | | | | |
| Negative | 56 (87.5) | 25 (67.6) | 126 (73.7) | 0.015 | 0.024 | 0.25 |
| Positive | 8 (12.5) | 12 (32.4) | 45 (26.3) | | | |
| Missing | 61 | 20 | 143 | | | |
| Triple negative | | | | | | |
| no | 57 (89.1) | 35 (94.6) | 151 (88.3) | 0.35 | 0.87 | 0.26 |
| yes | 7 (10.9) | 2 (5.4) | 20 (11.7) | | | |
| Missing | 61 | 20 | 143 | | | |

* The percents were calculated excluding those cancers with value unknown; P/NP, screen participants compared to non-participants; P/NI, screen participants compared to not invited; NP/NI, non-participants compared to not invited; ER, oestrogen receptor; PR, progesterone receptor; HER2, epidermal growth factor receptor 2

Table 2 – **Multivariable logistic regression for the association between clinicopathological characteristics of breast cancer and mode of participation (non-participants or not invited *versus* screening participants).**

| Parameters | OR adjusted for covariates | 95% Confidence Interval | P value |
|---|---|---|---|
| **Non participants/ Participants (n = 163)** | | | |
| Tumour size | | | |
| ↖20 mm | 1 | | |
| →20 mm | 4.36 | 2.00 – 9.71 | ←0.001 |
| Lymph nodes | | | |
| negative | 1 | | |
| positive | 1.28 | 0.58 – 2.83 | 0.54 |
| Tumour grade | | | |
| grade 1 | 1 | | |
| grade 2 | 0.78 | 0.28 – 2.19 | 0.64 |
| grade 3 | 2.30 | 0.71 – 7.45 | 0.17 |
| **Not invited/ Participants (n = 370)** | | | |
| Tumour size | | | |
| ↖20 mm | 1 | | |
| →20 mm | 2.39 | 1.38 – 4.13 | 0.002 |
| Lymph nodes | | | |
| negative | 1 | | |
| positive | 1.28 | 0.77 – 2.14 | 0.34 |
| ER status | | | |
| Positive | 1 | | |
| Negative | 1.12 | 0.47 – 2.69 | 0.79 |
| PR status | | | |
| Positive | 1 | | |
| Negative | 1.37 | 0.67 – 2.77 | 0.39 |

OR, odds ratio; ER, oestrogen receptor; PR, progesterone receptor

this last group cancers were slightly more positive for the hormonal receptors than in the not invited group, the difference was not significant ($P = 0.18$).

Information on HER2 status was missing for almost half of the cancers in participants and not invited women. The association between HER2 status and exposure/participation was statistically significant: negative status was more frequent in the participant group compared to non-participants or to not invited ($P = 0.015$ and $P = 0.024$, respectively). There were no significant differences according to exposure/participation status and the distribution of the triple-negative subtype.

In the multivariable analysis (table 2), 163 cases were included in the model for comparison of cancers in participants *versus* non-participants, and 370 cases for participants *versus* not invited group. Tumour size was the only significant variable in both final models. Larger tumours had higher probability to be found in cancers diagnosed in the group of non-participant ($P<0.001$) or not invited ($P=0.002$) groups compared to screening participants.

Information on treatment strategy was missing for 1.0% of participants, 12.3% of non-participants and 15.0% of not invited cases. When first treatment was surgery, the proportion of participants who underwent breast-conserving surgery was 57.4%, a value significantly higher compared to 34.1% of non-participants or 31.5% of not invited cancer cases ($P = 0.008$ and $P <0.001$, respectively). Chemotherapy as first treatment was recorded in 1.6% of participant women, which was significantly lower than 12.0%

among non-participants and 10.9% in the not invited group ($P = 0.003$ and $P = 0.002$, respectively).

## DISCUSSION

In the evaluation of an organized screening programme, it is of paramount importance to describe the clinicopathological features of the cancers detected. In this study, we assessed these characteristics among breast cancers detected in a rolling population-based organized screening programme, comparing them to the breast cancers detected by usual practice or non-organized screening activities. Ideally, comparison of prognostic factors such as size and stage should be presented as rates instead of proportions. However, the phased implementation of screening programme in the geographical region considered in this study hindered an accurate assessment of the population at risk and precluded the calculation of rates.

The results should be interpreted within the limitations imposed by the design of the study, the small sample size of the groups and missing values. Due to the small number of cancers in the participant group, we were not able to differentiate initial from subsequent screening round, which prevented a more in-deep analysis on the effect of length bias and overdiagnosis (Hakama *et al.*, 1995). To allow for a higher pool of cases and, consequently, a more relevant statistical power in the analyses performed, we used the maximum number of years of operation of the screening programme. Also, some variables had a considerable amount of missing values. Clinical information for non-participants in the screening program (either not invited or invited but not participating) was only available through linkage with the population-based cancer registry, which has a passive notification of cases by hospital and private practitioners. On the other hand, information on screening participants is actively collected due to the quality evaluation of the screening programme.

In an initial analysis (univariate), breast cancers were significantly smaller among screened participants, less prone to the development of axillary metastasis and were found in an earlier stage, compared to breast cancers in women invited but not participant, or compared to the experience of breast cancer in a population not exposed to organized screening. Stage migration (down-staging) is an expected effect of screening (Hofvind *et al.*, 2012). This result is in agreement with other studies, either hospital-based or population-based, using comparison groups defined in a variety of ways, from cancers detected only by symptoms or opportunistic screening, cancers detected in populations not participating or not yet offered screening, among others (Bucchi *et al.*, 2005; Baré *et al.*, 2006; Burke *et al.*, 2008; Mook *et al.*, 2011; Hofvind *et al.*, 2012; Nagtegaal & Duffy, 2013). Nevertheless, after multivariable analysis, size remained the only distinguishing characteristic of breast cancers detected within the screening programme compared to the other two studied groups. The small numbers in the multivariable analysis possibly hampered the disclosure of other significant associations. It is recognized that that expected benefit of early detection of breast cancer is not determined solely by tumour size but other variables as nodal status and grade are also significant (Narod, 2012).

It was not surprising that conservative surgery was more frequently done in the screening participants, in which, detected cancers were smaller and with a higher proportion of stage I. Adoption of less harmful and more effective treatments in areas where organized screening has been implemented is a recognized benefit of screening programmes (Berry *et al.*, 2005; Bulliard *et al.*, 2009; Hofvind *et al.*, 2012; Segnan *et al.*, 2012).

Breast cancers detected in the not invited group had a significantly smaller dimension compared to cancers detected in women who didn´t participate or were less compliant with the organized screening programme. Several authors have raised this issue of the impact of opportunistic screening among populations without an organized screening service (Bulliard *et al.*, 2009; Welch, 2010; Hoff *et al.*, 2012;

Vanier *et al.*, 2013). Opportunistic screening exists in the Northern Region of Portugal, though we have no precise estimates of its magnitude; furthermore, we were not able to assign individually, the participation in opportunistic screening for this group of women as it is recommended (Bulliard *et al.*, 2009). Not forgetting these limitations, it is legitimate to argue that opportunistic screening should have a stronger impact in the not invited group, as this was the only possibility for earlier diagnosis in this population, and a likely explanation for the differences in tumour size reported in this study. Also, the implementation of a screening programme in a region has been considered to trigger cancer awareness in patients outside the screening programme, with a prognostic benefit in these (Kalager *et al.*, 2009; Mook *et al.*, 2011; Domingo *et al.*, 2013). The above explanations are plausible and eventually consistent with our findings and those published by other authors who reported a worse prognosis, as presenting larger dimensions for tumours detected in non-participants (Duffy *et al.*, 1991; McCann *et al.*, 1998; Stockton & McCann, 2001; Hofvind *et al.*, 2012).

The number of breast cancer cases with missing data on tumour size, nodal status and grading was greater in the not invited group than in the other two groups. However, it is unlikely that relevant selection bias had been introduced, since age and period of diagnosis (between 2003-2005 or 2006-2008) of the women with missing information did not differ from the age and period of diagnosis of the other women.

Reasons for non-participation can vary along the period of implementation of a screening programme (Mook *et al.*, 2011; Nagtegaal *et al.*, 2011). In the beginning, most of the women not participating were not invited, but afterwards non-participation happens for other reasons such as worse accessibility and lower socioeconomic status (Mook *et al.*, 2011; Hofvind *et al.*, 2012); this may lead to selection biases in this type of study (Mook *et al.*, 2011; Hoff *et al.*, 2012). We minimized the likelihood of this bias, since we were able to constitute more homogenous groups of not participant and non invited women to be compared.

Breast cancers detected in screening participants and non-participants or not invited women, were all diagnosed in the same time frame, close geographical location in the northern region and reflected the full experience of breast cancer incidence in the population. Thus, the possibility of bias due to improvement in cancer diagnosis and treatment in more recent years or bias due to selection of the cases was probably reduced.

Using the information from the organized population-based screening programme and matching it with information from a population-based cancer registry with high completeness, favours the validity of the reported associations. That is because it is more likely that we have got almost complete information on the clinicopathological characteristics of breast cancers in populations exposed and not exposed to an organized screening programme.

Breast cancers detected in screening participants were significantly smaller and tumour size is considered one of the strongest predictors of breast cancer behaviour (Day *et al.*, 1989). As stated by others, the more favourable prognostic characteristics of the breast cancers detected in a population exposed to screening (including interval cancers) indicate an eventual mortality reduction in the future, due to this cause (Hofvind *et al.*, 2008; Bulliard *et al.*, 2009; Hofvind *et al.*, 2012; Kim *et al.*, 2012). Thus, though this is a limited descriptive study, its findings are consistent with an effective screening programme, which will have to be confirmed in future assessments. Therefore, more recent data will be published in part two of BCSP evaluation.

## DECLARATION OF CONFLICTING INTERESTS

Ana Aguiar was the Head of the Breast Cancer Screening Programme in the North Region of Portugal when the current study was performed. Vítor Veloso is the President of the Portuguese Cancer League, North Branch. For the remaining authors there are no conflicts of interest to disclose.

## ETHICS

This study has been approved by the Ethics Committee of the Institution within the work was undertaken (reference CES.mr.229.2013) and it conforms to the provisions of the Declaration of Helsinki.

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# TOTALLY IMPLANTABLE VENOUS ACCESS DEVICES IN ONCOLOGY: RETROSPECTIVE ANALYSIS OF 652 PATIENTS

## CATÉTERES VENOSOS CENTRAIS TOTALMENTE IMPLANTÁVEIS EM ONCOLOGIA: ANÁLISE RETROSPECTIVA DE 652 DOENTES

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**RESUMO**

**Introdução:** A presença de um acesso venoso adequado é essencial para o tratamento de doentes com cancro. A inserção de catéteres venosos centrais totalmente implantáveis (CVCTI) permite uma administração segura de quimioterapia, não sendo no entanto, isenta de complicações. O nosso objetivo é analisar a experiência do nosso centro no que respeita a utilização de CVCTI. **Materiais e Métodos:** Revisão dos registos médicos eletrónicos de todos os doentes com cancro que colocaram um CVCTI no Hospital da Luz, no período entre 1 de Janeiro de 2008 a 31 de Dezembro de 2014. **Resultados:** Analisaram-se retrospetivamente dados de 652 doentes com cancro. A incidência global de complicações foi 14.1% (91), sendo apenas 0.9% (6) complicações precoces (antes da primeira utilização do CVCTI). As complicações trombóticas (30, 4.5%) e infecciosas (cutâneas e associadas ao CVCTI, 24, 3.5%) foram as mais frequentes, seguindo-se a exteriorização (13, 1.9%) e disfunção do catéter (11, 1.6%). Removeram-se 155 CVCTI, a maioria (95, 61.3%) após o fim do tratamento, e os restantes devido a complicações (60; 38.7%). **Discussão:** A taxa global de complicações foi de encontro ao esperado, havendo no entanto um baixo número de complicações precoces e nenhuma complicação potencialmente fatal associada ao procedimento foi identificada. Ao contrário do expectável as complicações trombóticas foram as mais frequentes, seguindo-se as infecciosas. **Conclusões:** A inserção de CVCTI em doentes com cancro é um procedimento seguro, com uma taxa baixa de complicações sem nenhum evento fatal identificado neste estudo.

***Palavras-chave:*** *Neoplasia; Quimioterapia; Cateteres venosos totalmente implantáveis.*

**ABSTRACT**

**Introduction:** Adequate venous access is essential for the treatment and management of cancer patients. Insertion of totally implantable venous access devices (TIVADs) provide a safe method for chemotherapy (ChT) administration, but it's not free of complications. We aim to analyze our institution clinical practice experience regarding TIVADs. **Materials and Methods:** Electronic medical records (EMR) review of all cancer patients that required placement of a TIVAD at Hospital da Luz between January 1st 2008 and December 31st 2014. **Results:** Clinical data from 652 cancer patients was retrospectively reviewed. The overall incidence of complications was 14.1% (91), with only 6 (0.9%) being early complications (before the first clinical TIVAD utilization). The most common complications were thrombosis (30, 4.5%) and infections (TIVAD related and cutaneous, 24, 3.5%), followed by exteriorization (13, 1.9%) and catheter dysfunction (11,1.6%). 155 TIVADs were removed, the majority (95, 61.3%)

because of end of treatment and the remainder (60; 38.7%) due to catheter complications. **Discussion:** Global complication rate was as expected, however we observed a low rate of early complications, and we didn't observe any potentially fatal complication related to the procedure. Unlike expected, thrombotic complications were the most frequent, followed by infectious complications. **Conclusions:** TIVADs insertion is a safe procedure in cancer patients with an apparent low rate of complications with no fatal events identified in this study.

***Keywords***: *Neoplasms; Chemotherapy; Totally implantable catheters.*

## INTRODUCTION

Totally implantable venous access devices (TIVADs) of long duration are widely used in cancer patients worldwide. They allow a safer administration of cytotoxic medication and provide an easier and more comfortable venous access for blood samples, transfusions and other needed medications. While placed under local anesthesia and as an outpatient procedure, TIVADs can be associated with complications that need to be recognized and treated. Early complications refer those ones directly related to its insertion and include pneumothorax, hemothorax, air embolism, accidental arterial puncture, cardiac arrhythmia, cardiac tamponade, brachial plexus injury, hematoma, infection of surgical wound and catheter dysfunction. Late complications include bloodstream infection, catheter-site infection, thrombosis, catheter dysfunction, rupture, migration or embolization, exteriorization, port inversion, superior vein cava erosion and perforation. The total complication rate varies between 8 and 38% in recent published retrospective analysis, with infections and thrombosis being the most frequent.[1,2,3,4]

The aim of this study was to evaluate our institutional clinical practice experience regarding TIVADs associated complications in cancer patients.

## MATERIALS AND METHODS

This study is a retrospective review of the EMR of all cancer patients in which a TIVAD was inserted for chemotherapy administration, at Hospital da Luz, Lisbon, between January 1st, 2008 and December 31st, 2014. The study was performed according to the principles of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the Institution. Waiver of Informed Consent was requested by the investigators and approved by the Ethics Committee due to the retrospective noninterventional nature of the study. The study population was identified by cross-referencing the list of patients who placed TIVAD with the list of patients with a diagnosis of cancer. We reviewed the medical records and collected data regarding gender, age, cancer diagnosis and stage (locoregional *versus* metastatic), anatomic site of venous access placement of TIVAD, duration of TIVADs, causes of replacement/removal and other complications. The complications were assessed until April 2015. We also reviewed the reports of all upper extremity venous Doppler ultrasounds, thoracic and neck computed tomography (CT) angiographies and pulmonary ventilation/perfusion scans of those patients in order to evaluate the incidence of catheter related thrombosis and pulmonary thromboembolism in the study population.

All TIVADs were inserted by a general surgeon of Hospital da Luz, the majority under local anesthesia as an outpatient regimen. No TIVAD was inserted in the presence of fever, known systemic infection or inflammatory signs at the site of insertion. Two types of TIVADs were used, both from B.Braun manufacturer: Celsite implantofix standard F8.5 and F10. Prior to placement, a complete blood count with platelets and coagulation tests (PT and aPTT) were performed to ensure the safety of the procedure. Right

subclavian vein was the preferred venous access site, due to surgeon´s preference, to greater ease of insertion and shorter distance to the superior vena cava and right atrium. However, left subclavian vein or jugular veins were chosen in patients who underwent right-sided mastectomy, radiotherapy or in whom the right sided approach was unsuccessfully attempted. After insertion, the correct location and potential early complications were ascertained by chest x-ray. The catheter was ready to be used 24-48h after insertion and maintained with routine flushing with saline and heparin after each manipulation with a maximum interval of 6 to 8 weeks.

For this study, TIVAD *infection* was defined as the presence of inflammatory signs on the site of the TIVAD placement with positive blood cultures drawn from the TIVAD. In the presence of inflammatory signs on the site of the TIVAD, with negative or absent blood cultures it was classified as *cutaneous infection of the TIVAD site. Systemic infection* was defined as absence of local signs of TIVAD infection, positive peripheral blood cultures, with or without positive blood culture drawn from the TIVAD, with an identified source of infection other than the TIVAD. *Febrile syndrome* was referred as persistent fever with no clinical source identified and negative blood cultures after appropriate etiological investigation. *Catheter associated thrombosis* was defined as thrombotic occlusion of the catheter with involvement of the vein where the catheter was placed, as documented by Doppler ultrasound or CT angiography. *Catheter obstruction* was related to intraluminal obstruction without extension to the vein, reservoir rotation, misplacement, pinch-off syndrome or disconnection. *Catheter disfunction* was considered if there was persistent inability to inject fluid and/or aspirate blood through the TIVAD without an identified cause. Venous thromboembolism was defined as a ventilation-perfusion mismatch in lung scintigraphy or a filling defect within the pulmonary vasculature in CT angiography. No routine examinations were performed to identify thrombosis, unless there was clinical suspicion.

Complications were subdivided in *early complications* (associated with the procedure or occurring up to the first catheter utilization) and *late complications* (after first catheter use).

Statistical analysis was performed using both Microsoft Excel and SPSS 23.0 software. Continuous data are expressed as medians and ranges, while categorical variables are expressed in frequencies and percentages. Categorical data were compared by Fisher's exact test.

## RESULTS

Between January 1st 2008 and December 31st 2014, 681 TIVADs were inserted in 652 cancer patients, with a median age of 60 years-old (minimum 17, maximum 89), 431 (66%) in women. The most frequent anatomic site for venous access was right subclavian vein (601, 88.3%) followed by left subclavian vein (56, 8.2%) and right jugular vein (17, 2.5%) (Table I).

Table I – **Characteristics of the study population**

| Total Patients / TIVADs | 652/681 |
|---|---|
| Gender (Male:Female) | 221:431 |
| Age (median, range) | 60 (17-89) |
| Anatomic site of venous access | 681 |
| Right subclavian vein | 601 (88.3%) |
| Left subclavian vein | 56 (8.2%) |
| Right jugular vein | 17 (2.5%) |
| Left jugular vein | 4 (0.6%) |
| Right cephalic vein | 2 (0.3%) |
| Left femoral vein | 1 (0.1%) |

The majority of patients had solid tumors, only 14 (2.9%) had hematologic malignancies. The most common cancer diagnoses were colorectal (30.4%), breast (24.5%), pancreas (8.3%), lung (7.4%) and stomach (6.4%). Among patients with solid tumors 394 (60%) patients had locoregional disease *versus* 244 (37%) who had metastasis.

A total of 155 (22.8%) TIVADs were removed after a median duration of 375 days (minimum 6, maximum 2763). The main reason for catheter removal was the end of cancer treatment (95, 14%) followed by catheter associated complications in 60 (8.8%) patients, including, exteriorization (13, 1.9%), disfunction (11, 1.6%), thrombosis (9, 1.3%), infection (8, 1.2%), obstruction (7, 4.5%), febrile syndrome (6, 3.9%), cutaneous infection (3, 1.9%), systemic infection (2, 1%), brachial plexus injury (1, 0.15%).

There were 96 (14.1%) complications documented in the study population, of which 6 (0.9%) were early complications and 90 (13.2%) late complications (Table II). None resulted in death of a patient.

Table II – **TIVAD Complications**

| Complications | N (%) |
|---|---|
| **Total** | 96 (14.1%) |
| **Early complications** | 6 (0.9%) |
| TIVAD infection | 2 (0.3%) |
| Hematoma | 2 (0.3%) |
| Brachial plexus injury | 1 (0.1%) |
| Dysfunction | 1 (0.1%) |
| **Late complications** | 90 (13.2%) |
| TIVAD thrombosis | 30 (4.5%) |
| Cutaneous infection | 15 (2.2%) |
| Exteriorization | 13 (1.9%) |
| Dysfunction | 10 (1.5%) |
| Obstruction | 7 ( 1.0%) |
| TIVAD infection | 7 (1.0%) |
| Febrile syndrome | 6 (0.9%) |
| Sepsis | 2 (0.3%) |

The incidence of catheter related thrombosis was 4.4% (30 patients). This subgroup had a median age of 59 years-old (minimum 29, maximum 82), most of them women (21, 70%) with all TIVADs implanted on the subclavian vein (77% on the right side, 23% on the left side); 58% had metastatic disease and the most frequent cancer diagnosis were colorectal (9 out of 198), breast (6 out of 166), stomach (3 out of 42), pancreas (3 out of 54), lung (2 out of 48), ovary (2 out of 35) and occult primary (2 out of 14). Thrombosis was diagnosed a median of 75 days after TIVAD insertion (minimum 7 days, maximum 1600 days). In 3 cases (10%) thrombosis was an isolated imaging finding (detected on a procedure requested for non-TIVAD related reasons), thus the incidence of symptomatic thrombosis was 4% (27). The most common clinical presentation was upper limb edema (18 patients, 60%) followed by pain (11, 36,7%), neck edema (6, 20%), collateral venous circulation (5, 16.7%), difficulty with injection/aspiration of fluids (2, 6.7%) and superior vena cava syndrome (2, 6.7%). None of these patients was under prophylactic anticoagulation and all of them were treated with therapeutic doses of low molecular weight heparin (LMWH) after confirming the diagnosis on an imaging exam. However, it was deemed necessary to remove the catheter in 9 cases (30%).

We identified 13 cases of pulmonary embolism (PE) in 652 patients with TIVADs (incidence of 2%), 3 had concomitant catheter related thrombosis (3 out of 30 (10%) patients with catheter related thrombosis; p=0,0184, Fisher's exact test). All 3 patients had metastatic disease, 2 from colon cancer (none on Chemotherapy (ChT) or within 6 months of surgery), and 1 with a recent diagnosis of lung cancer (< 6 months) on ChT.

TIVAD infection was observed in 9 cases (incidence of 1.3%) with the following isolated microorganisms: *Pseudomonas aeruginosa* (3), Methicillin-resistant *Staphylococcus aureus* (3), *Enterococcus faecalis* (1), *Staphylococcus epidermidis* (1), *Klebsiella pneumonia* (1).

There were 7 cases of non-thrombotic TIVAD obstruction due to misplacement (3 cases), reservoir rotation (2 cases), catheter disconnection from the reservoir (1 case) and pinch-off syndrome (1 case) were documented. TIVAD dysfunction was reported in 11 cases (1.6%).

## DISCUSSION

Since the first report on TIVADs insertion in 1982 by Niederhuber et al. many studies have demonstrated their safety and clinical benefit in patients with cancer.[5] TIVADs became a fundamental part in the treatment of these patients as they reduced the number of complications related to chemotherapy administration and allowed a better quality of life. Despite its undeniable advantages, the use of TIVADs is associated with potentially serious complications. In this series we report a total of 96 (14.1%) complications, with infections and catheter related thrombosis accounting for 56.3% of the total (24 infections and 30 catheter related thrombosis). Our results are comparable to most recent publications, which report complication rates between 8 and 38%.[1,2,3,4] However, it should be noted that the number of early complications was less than expected (6, 0.9%), since previous studies report rates between 1.8% and 26.8%.[6] This can be explained, at least in part, by the fact that insertion of TIVADs is a standardized procedure performed by a specialized team, but we must acknowledge this is a retrospective analysis subject to potential limitations in data documentation. Nevertheless, it's important to point out that we didn't observe any potentially fatal complication related to the procedure such as pneumothorax, hemothorax, air embolism or cardiac tamponade.

Infections are the most frequently reported catheter related complications, yet, in this series, thrombosis was the most common. Even if we consider TIVAD related infection and cutaneous infection together the incidence is still lower than thrombosis (24, 3.5% versus 30, 4.5%). In the literature, the rate of symptomatic thrombosis ranges from 2 to 8%, however, if routine screening is performed with Doppler ultrasound in asymptomatic individuals the incidence increases to 27-66%.[4,6,7,8,9] Accordingly, our results fit into the expected with a symptomatic thrombosis rate of 4.1%. If we consider Virchow's triad it's easy to understand the high risk of thrombosis in these patients, considering the hypercoagulability state related with cancer and the endothelial lesion promoted either by ChT and the TIVAD. There is an association between catheter related thrombosis and PE. Given that catheter related thrombosis is one of the commonest complications of TIVADs, prophylaxis with anticoagulants has been studied with inconclusive results and is not recommended. Treatment guidelines for catheter related thrombosis recommend at least three months of LMWH or LMWH followed by warfarin (INR, 2.0 to 3.0), with total duration depending on clinical characteristics of individual patients. Although it is appropriate to try treat thrombosis without catheter removal, if there are contraindications to anticoagulant medication, persistent or worsening symptoms, infection or TIVAD dysfunction, catheter removal must be considered. In this series only the 2 patients presenting with superior vena cava syndrome had their catheter immediately removed. The remainder were treated with LMWH, with 7 patients with persistence or worsening symptoms had their catheter removed. Concerning routine catheter management only saline flushing is indicated by guidelines, with insufficient data supporting routine use of anticoagulants to prevent catheter occlusion. [6] However in our institution TIVADs have been managed with heparin infusion.

Infectious complications were the second most frequent complication. They are a matter of concern as cancer patients are immunocompromised by the disease and its treatment, therefore more susceptible to develop sepsis. Reported rates of catheter associated infections can be as high as 31%, with lower rates in recent series (around 2%). These data are difficult to compare due to great variability between studies in the diagnostic criteria used to define catheter related infection. Coagulase-negative staphylococci are usually the most frequent identified microorganisms in patients with cancer and a catheter and initial empiric selection of antimicrobial agent should include a third-generation cephalosporin or vancomycin.[2,10] However in our series, *Pseudomonas*

*aeruginosa* and Methicillin-resistant *Staphylococcus aureus* accounted for more than half of the microorganisms isolated. Infection is considered an indication for TIVAD removal except if there aren't any local signs of infection, blood cultures are negative after 48-72hours of antimicrobial treatment, patients are hemodynamically stable and there is no infection relapse with the same agent after the first course of antimicrobials.[6] In this series 15 cutaneous infections were identified, the majority managed with oral antimicrobial therapy, with only 3 TIVADs removed due to lack of response or relapse of infection.

Regarding non-thrombotic causes of TIVAD obstruction it is important to identify possible causes for the malfunction, namely, the pinch off syndrome in catheters placed in the subclavian vein, where changing the arm and shoulder position can sometimes overcome the catheter dysfuncion. If there is difficult in aspiration of blood but maintained infusion capacity, changing the patient's position can also help if the catheter tip is positioned against the vein wall. Even if this malfunction cannot be overcome, in most cases TIVAD is maintained for ChT administration, collecting blood samples from a peripheral vein.

## CONCLUSION

TIVADs are safe and provide benefits for patients with cancer undergoing systemic iv treatment, with a low risk of associated complications. As others, we also report a low rate of complications with no fatal events. A multidisciplinary effort must be made to minimize these complications by the promotion of a correct insertion technique, TIVAD aseptic management and optimized patient follow up.

However, since this is a retrospective study, we have to acknowledge potential limitations, including, under-reporting of complications, lack of optimal documentation of clinical information and empiric treatment with antimicrobials without previous blood cultures.

## ABBREVIATIONS LIST

TIVAD: Totally implantable venous access devices
CT: Computed tomography
EMR: Electronic medical records
LMWH: low molecular weight heparin
PE: pulmonary embolism
ChT: Chemotherapy
IV: intravenous

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# COLECISTOSTOMIA PERCUTÂNEA NO TRATAMENTO DA COLECISTITE AGUDA LITIÁSICA

## PERCUTANEOUS CHOLECYSTOSTOMY IN THE MANAGEMENT OF CALCULOUS ACUTE CHOLECYSTITIS

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**ABSTRACT**

**Background:** Laparoscopic cholecystectomy is the gold-standard treatment in acute cholecystitis. However, percutaneous cholecystostomy stands as an alternative therapeutic approach among the elderly or patients with several comorbidities. **Objective:** The aim of this study is to clarify the role of percutaneous cholecystostomy in calculous acute cholecystitis treatment and to elucidate about its association with the surgical treatment. **Methods:** In December 2016, a systematic database search on PubMed, Scopus and Web of Science was conducted to identify articles on percutaneous cholecystostomy published from January 2013 to November 2016, using the query "(acute cholecystitis OR severe cholecystitis) AND (cholecystostomy OR percutaneous cholecystostomy OR cholecystostomy tube)". In total, 290 articles were found and then submitted to inclusion and exclusion criteria. **Results:** A total of 13 records involving 1130 patients from 10 different countries met all inclusion criteria and were therefore included in this systematic review. All studies found eligible concluded percutaneous cholecystostomy is a potentially safe and effective therapeutic approach among high-risk surgical patients in the setting of acute cholecystitis. Percentage of patients undergoing percutaneous cholecystostomy followed by cholecystectomy varied between 7.2% and a maximum of 66.7%, with a conversion rate fluctuating between 0.0% and 66.7%. Complication and mortality rates ranged from 2.2% to 41.7% and 0.0% and 43.2%, respectively. **Conclusions:** Percutaneous cholecystostomy is generally considered safe and effective among high-risk surgical patients diagnosed with acute cholecystitis.

***Keywords:*** *Acute Cholecystitis; Cholecystostomy; Cholecystectomy.*

**RESUMO**

**Introdução:** A colecistectomia laparoscópica é considerada gold-standard no tratamento da colecistite aguda. Contudo, a colecistostomia percutânea surge como alternativa terapêutica em doentes idosos ou com várias comorbilidades. **Objetivo:** O objetivo deste estudo é clarificar o papel da colecistostomia percutânea no tratamento da colecistite aguda litiásica, bem como

[*] Estes autores contribuiram de igual forma para este trabalho.

esclarecer a sua associação com o tratamento cirúrgico. **Métodos**: Em dezembro de 2016, foi realizada uma pesquisa sistemática nas bases de dados PubMed, Scopus e Web of Science, no sentido de identificar artigos sobre colecistostomia percutânea publicados entre janeiro de 2013 e novembro de 2016, com recurso à query "(acute cholecystitis OR severe cholecystitis) AND (cholecystostomy OR percutaneous cholecystostomy OR cholecystostomy tube)". No total, foram encontrados 290 artigos, os quais foram submetidos a critérios de inclusão e exclusão. **Resultados:** No total, 13 artigos envolvendo 1130 pacientes de 10 países diferentes cumpriram todos os critérios de inclusão, tendo sido incluídos na presente revisão sistemática. Todos os estudos considerados elegíveis concluíram que a colecistostomia percutânea é uma abordagem terapêutica potencialmente segura e eficaz em pacientes de alto-risco cirúrgico no contexto de colecistite aguda. A percentagem de pacientes que receberam colecistostomia percutânea e subsequente colecistectomia variou entre 7.2% e um máximo de 66.7%, com uma taxa de conversão entre 0.0% e 66.7%. As taxas de complicações e mortalidade variaram entre 2.2% a 41.7% e entre 0.0% a 43.2%, respetivamente. **Conclusões:** A colecistostomia percutânea é um procedimento considerado, na generalidade, seguro e eficaz em pacientes de alto-risco cirúrgico diagnosticados com colecistite aguda.

***Palavras-chave:*** *Colecistostomia; Colecistite Aguda; Colecistectomia.*

## INTRODUCTION

Acute cholecystitis, an inflammatory condition affecting the gallbladder, mainly associated to lithiasis, stands as one of the most relevant surgical causes of emergency hospital admissions [1,2].

Laparoscopic cholecystectomy has been defined as the gold-standard therapeutic approach, with recommendations highlighting the importance of an early surgical intervention as soon as the diagnosis is established[3].

While very common, acute cholecystitis in the elderly and comorbid populations may have an atypical symptomatic presentation and further complicate, prompting difficult surgical treatment[4]. Agnieszka Popowicz et al. point out early cholecystectomy in high-risk patients might be associated with significant morbidity and mortality[5]. In fact, the intrinsic vulnerability of patients of an advanced age and several comorbidities may negatively impact on surgical outcomes, with perioperative morbidity and mortality rising up to 41% and 18%, respectively[1].

Pioneered by R.W. Radder in the 80s[5], ultrasound-guided percutaneous cholecystostomy consists of a minimally invasive procedure under local anaesthesia, and is generally considered safe[5,6].

According to Wang et al., symptomatic relief up until 72 hours has been registered among more than 80% of patients submitted to cholecystostomy, as well as a procedure-associated mortality being inferior to 3%[1]. Therefore, percutaneous cholecystostomy may play an increasingly important role in treating severe acute cholecystitis diagnosed in high-risk surgical patients, with substantial co-morbidities[6]. Moreover, performing percutaneous cholecystostomy in patients not eligible for surgery at the time of diagnosis may not only serve as bridging therapeutic approach between medical treatment and surgery, but also as a potentially definitive treatment measure[5]. Indeed, Ye Rim Chang et al. indicate 88.3% of high-risk surgical patients who underwent percutaneous cholecystostomy showed no relapse during a follow-up period of almost two years[7].

Notably, the procedure has been applied to decreasingly co-morbid patients recently[1,8]. In fact, comparing trends of percutaneous cholecystostomy use, Travis Smith et. al reveal only ASA III and IV patients were submitted to drainage the decade before 1995, whereas only 80% were received such high ASA classifications when receiving the procedure the decade after[8], with mortalities having dropped from 22.1% to 13.3% since that time[8]. Such improved mortality rate may put in evidence the importance of patient selection when deciding on cholecystostomy indication[8].

However, the role of cholecystostomy as an alternative treatment option to early cholecystectomy remains poorly established[5]. Campanile et al.

enhance the need of further investigation on the field in order to clarify its importance and indication criteria, given the heterogeneity in defining high-risk surgical patients[3]. Besides, literature is not consensual regarding performance of an elective laparoscopic cholecystectomy subsequently to percutaneous cholecystostomy, nor as far as the precise time interval between drainage and surgery is concerned[3].

According to the widely used 2013 Tokyo Guidelines, severe acute cholecystitis cases treated with percutaneous cholecystostomy must be only submitted to cholecystectomy three months later[6]. Yet, different studies highlight the advantages of early surgery even in patients of worse surgical profiles. In a systematic review published in 2009, Windbladh et al. describe higher post-cholecystostomy mortality when compared to early cholecystectomy in non-surgical patients, again emphasizing the need of clinical trials on the subject[9]. Moreover, Campanile et al. claim in-hospital mortality associated with cholecystostomy is said to vary between 4 and 50%, signalling study limitations on this matter and how each investigation might define high-risk surgical individuals in divergent manners[3]. Also, need for surgery has been less investigated than conservative management, particularly in high surgical risk patients[3].

Given the absence of consistent evidence in literature on how and when to recommend percutaneous cholecystostomy in the treatment of acute cholecystitis, this systematic review aims to help validate this procedure as a therapeutic approach, to precise its potential indications and to clarify its association with the surgical treatment.

## METHODS

In December 2016, a literature search was performed to identify studies focusing on the role of percutaneous cholecystostomy as a treatment option for acute cholecystitis.

A systematic search on PubMed, Scopus and Web of Science was conducted spanning from January 2013 to November 2016. Studies were identified using the following query: "(acute cholecystitis OR severe cholecystitis) AND (cholecystostomy OR percutaneous cholecystostomy OR cholecystostomy tube)". Only studies in humans were considered.

A total of 290 articles were initially retrieved, 110 from PubMed, 25 from Scopus and 155 from Web of Science. Repeated articles among different databases were excluded, remaining 167 records for assessment. Reference lists of eligible articles were hand-searched.

All articles written in languages other than Portuguese or English were excluded, as well as reviews, clinical cases, editor letters or video articles. Additionally, articles about acute acalculous cholecystitis or other conditions other than acute cholecystitis or associated with a malignant etiology were also excluded. Finally, studies involving less than thirty patients were considered small unrepresentative sample populations, having been set aside too. Therefore, from 167 records assessed, 36 full-text articles were assessed for eligibility.

Inclusion criteria were as it follows: populations which were fully characterized according to gender, mean age and American Society of Anaesthesiologists (ASA) physical status classification system, further including information on percutaneous cholecystostomy indication, outcomes of percutaneous cholecystostomy, outcomes of an eventual procedure of cholecystectomy following percutaneous cholecystostomy, procedure-associated complications, global mortality and eventual re-admissions.

Following these criteria, 23 from 36 studies were excluded, and the remaining 13 papers were included in this systematic review. All sequential steps comprising the abovementioned process are depicted in Figure 1.

## RESULTS

Among 13 articles found eligible, all studies stressed the effectiveness and safety of percutaneous cholecystostomy as a symptomatic therapeutic

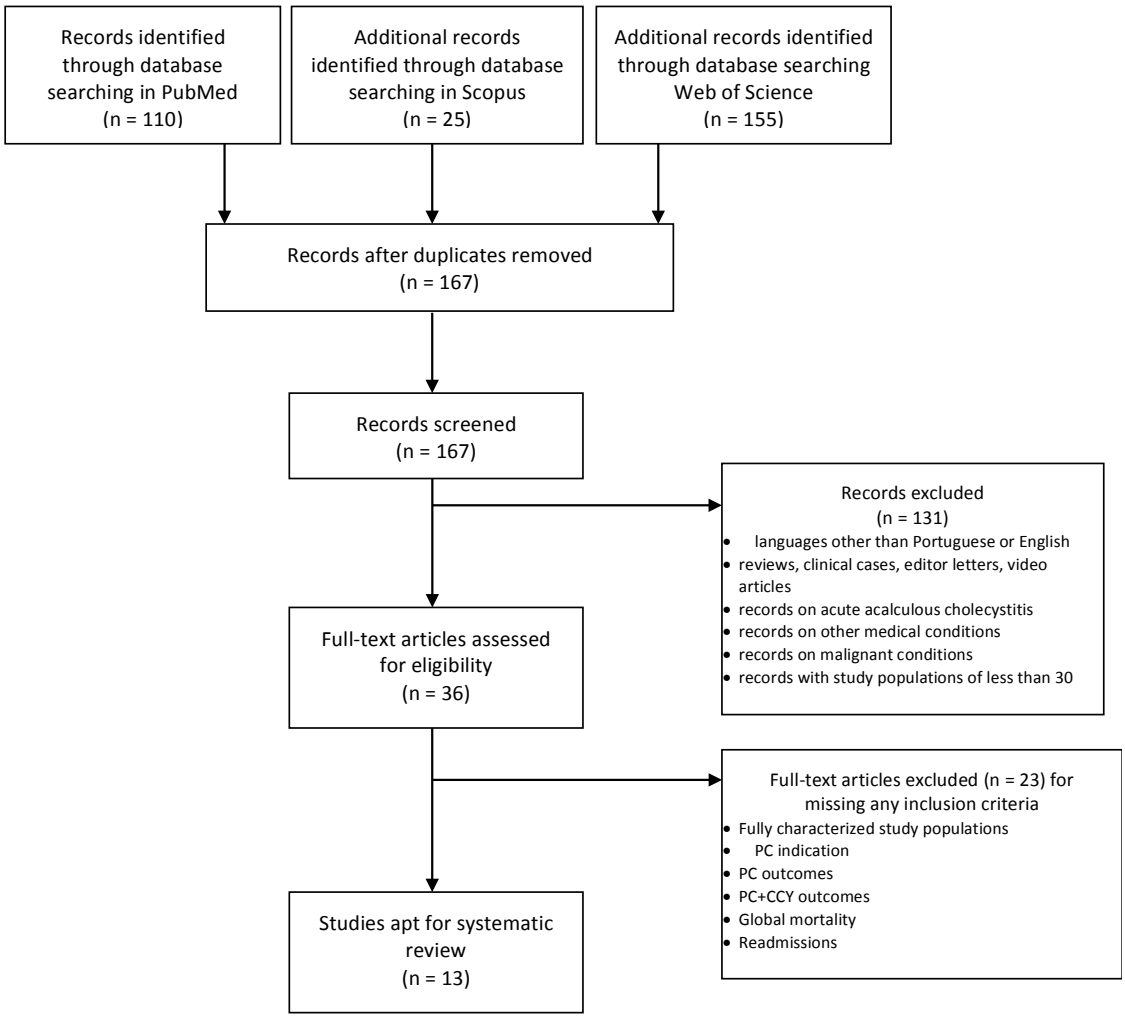


FIGURE 1 – **Flow diagram representing methods for data analysis throughout all phases of this systematic review. Abovementioned are discriminated all articles found, included and excluded, and exclusion criteria applied. PC, percutaneous cholecystostomy; PC+CCY, percutaneous cholecystostomy followed by cholecystectomy.**

approach among high-risk patients, as in bearing less favourable surgical profiles.

A total of 1130 patients prevenient from 10 different countries were counted. Characterization of all 13 study populations is depicted in Table 1.

Reported outcomes are covered by Table 2 and specific considerations made about each study were as it follows.

Travis J. Smith et al. described an association between percutaneous cholecystostomy tubes placement and elderly age and increased number of comorbidities[8], namely cardiovascular disease (66% vs 26%, p = 0.001), diabetes (27% vs 13%, p = 0.001), and mean Charlson comorbidity index (3.27 vs 1.07, P = 0.001). Retrospectively comparing trends of cholecystostomy performance during the 90s versus the 00s, authors also observed global decreasing mortality rates[8], with mortality at 30-day follow-up lowering from 36% to 12% among patients submitted to drainage (p = 0.001).

According to Chung-Kai Chou et al., patients diagnosed with acute severe cholecystitis who were considered unfit for surgery and underwent early percutaneous cholecystostomy showed declining

Table 1 – **Characterization of all 13 study populations according to year of publication, country of origin, design of study (R – retrospective; P – prospective), number of patients included, female to male ratio (F:M), mean age of patients (in years) and number of patients corresponding to an American Society of Anaesthesiologists (ASA) score equal or superior to 3.**

| Study | Year | Country | Design | Number of patients | F:M | Mean age, years | Number of patients with ASA↗3 |
|---|---|---|---|---|---|---|---|
| *Qingming Ni et al.* | 2015 | China | R | 62 | 34:28 | 72.1 | 44 (71.0%) |
| *Charleen Shan Wen Yeo et al.* | 2015 | Singapore | R | 103 | 46:57 | 80 (43-105) | 88 (85.4%) |
| *Chung-Kai Chou et al.* | 2015 | Taiwan | R | 209 | 60:149 | 74.54 | 200 (95.7%) |
| *Asgaut Viste et al.* | 2015 | Norway | R | 104 | 47:57 | 73.5 (22-96) | 44 (42.3%) |
| *Won Seok Janga et al.* | 2014 | South Korea | R | 93 | 52:41 | 73.8 ± 12.1 | 48 (51.6%) |
| *Enver Zerem et al.* | 2014 | Bosnia and Herzegovina | R | 36 | 24:12 | 75 ± 9.7 | 25 (72.2%) |
| *E. Atar et al.* | 2014 | Israel | R | 81 | 33:48 | 82 (47-99) | 81 (100%) |
| *Byung Hyo Cha et al.* | 2014 | South Korea | R | 82 | 39: 43 | 72.1 ± 13.7 | 82 (100%) |
| *Mehrdad Nikfarjam et al.* | 2013 | Australia | P | 32 | 16:16 | 78 (45-97) | 32 (100%) |
| *Khang Wen Pang et al.* | 2016 | Singapore | R | 71 | 28:43 | 73 (38-96) | 71 (100%) |
| *Wei-Chen Lin et al.* | 2016 | Taiwan | R | 61 | 30:31 | 80.3 ± 9.3 | 58 (95.1%) |
| *Pandanaboyana Sanjay et al.* | 2013 | New Zealand | R | 53 | 21:32 | 74 (14-93) | 49 (92.5%) |
| *Travis J. Smith et al.* | 2013 | EUA | R | 143 | 50:93 | 72.0 ± 13.5 | 117 (81.8%) |

Table 2 – **Outcomes of all 13 studies included, i.e. number of patients who underwent percutaneous cholecystostomy only (PC only), number of patients who underwent percutaneous cholecystostomy followed by cholecystectomy (PC+CCY), conversion rate to open cholecystectomy, number of all complications recorded, global mortality observed and number of readmissions registered. Symbol – stands for no information available.**

| Study | | PC only | PC+CCY | Conversion rate | Complications | Mortality | Readmissions |
|---|---|---|---|---|---|---|---|
| *Qingming Ni et al.* | | 36 | 26 (41.9%) | 19.2% | 3 (4.8%) | 0 (0.0%) | 4 (6.4%) |
| *Charleen Shan Wen Yeo et al.* | | 61 | 42 (40.7%) | 15.0% | 10 (9.7%) | 13 (12.6%) | 7 (6.8%) |
| *Chung-Kai Chou et al.* | | 101 | 95 (45.5%) | - | 26 (12.4%) | 13 (6.2%) | 20 (9.6%) |
| *Asgaut Viste et al.* | | 70 | 30 (28.8%) | 7.7% | 13 (12.5%) | 4 (3.8%) | 0 (0.0%) |
| *Won Seok Janga et al.* | | 31 | 62 (66.7%) | 3.2% | 2 (2.2%) | 2 (2.2%) | 6 (6.5%) |
| *Enver Zerem et al.* | | 23 | 6 (16.7%) | 16.7% | 15 (41.7%) | 7 (19.4%) | 5 (13.9%) |
| *E. Atar et al.* | | 10 | 36 (44.4%) | 11.1% | 6 (7.4%) | 35 (43.2%) | 2 (2.5%) |
| *Byung Hyo Cha et al.* | | 47 | 35 (42.7%) | 0.0% | 2 (2.4%) | 2 (2.4%) | 0 (0.0%) |
| *Mehrdad Nikfarjam et al.* | | 21 | 9 (28.1%) | 0.0% | 6 (18.8%) | 3 (9.4%) | 14 (43.8%) |
| *Khang Wen Pang et al.* | | 33 | 32 (45.1%) | 11.5% | 20 (28.2%) | 23 (32.4%) | 7 (9.9%) |
| *Wei-Chen Lin et al.* | *Group 1 (non-elderly)* | 7 | 23 (7.2%) | 8.7% | 5 (15.6%) | 2 (6.2%) | 2 (6.2%) |
| | *Group 2 (elderly)* | 19 | 34 (55.7%) | 17.6% | 16 (26.2%) | 8 (13.1%) | 8 (13.1%) |
| *Pandanaboyana Sanjay et al.* | | 23 | 18 (34.0%) | 66.7% | 7 (13.2%) | 12 (22.6%) | 13 (24.5%) |
| *Travis J. Smith et al.* | | 67 | 59 (41.3%) | 14.0% | 21 (14.7%) | 17 (11.9%) | 0 (0.0%) |

hospital length of stay (15.8 ± 12.9 vs 21.0 ± 17.5 days in patients with late procedure) and procedure-related bleeding (0.0% vs 5.0%, p = 0.018)[10].

Asgaut Viste et al. highlight only minor complications related to the procedure (reported among 12.5% patients) with predominant successful tube insertion and rapid symptom relief experienced in 97% of individuals who enrolled in the study[11]. E. Atar et al. put in evidence very satisfying rates of technically successful procedures, with effective tube insertion among all 81 critically ill patients and no reports of major complication events[12].

Furthermore, cholecystostomy showed to improve survival among high-risk individuals included in a study led by Charleen Shan Wen Yeo et al., with emphasis on the importance of early procedure for outcome improvement. Indeed, authors describe that cholecystostomy was performed at a median of 2 days after establishing acute cholecystitis diagnosis, avoiding high failure rates mentioned in literature[13].

As far as how cholecystostomy might be related with subsequent surgery, a Norwegian retrospective analysis conducted by Asgaut Viste et al. concluded that only one-third of 104 patients submitted to percutaneous biliary drainage were later cholecystectomized[11]. Moreover, Enver Zerem et al. affirm high-risk surgical patients might not even need further treatment once percutaneous cholecystostomy is performed[14]. E. Atar et al. also focus on the efficacy of conservatively treating critical patients with acute cholecystitis, stating that surgical outcomes after percutaneous cholecystostomy are superior to those of cholecystectomy only[12]. Dividing and comparing patients in two subsets according to their age (group 1 corresponding to non-elderly patients, age ≤ 70 years, and group 2 including all elderly patients, age > 70 years), Wei-Chen Lin et al. conclude high-risk elderly and substantially comorbid patients should be early identified as such and submitted to cholecystostomy, as they may benefit not only from better clinical outcomes, with a decrease in hospital length of time and associated morbidity, but also from better eventual surgical outcomes, enabling effective performance of delayed laparoscopic cholecystectomy[15]. Byung Hyo Cha et al. further define percutaneous cholecystostomy as the best definitive therapeutic option for those with acute cholecystitis who are not eligible for surgery at diagnosis, adding that certain cases may be appropriate for safe drainage tube removal[16].

When investigating which post-drainage clinical circumstances might predict eventual later surgery, Won Seok Janga et al. found advanced patient age, higher increased American Society of Anaesthesiologists (ASA) score and history of cerebrovascular accident (CVA) to be statically significant risk factors[17].

Despite all defending cholecystostomy as safe and effective in treating severe cases of acute cholecystitis, five of thirteen studies made remarks on possible conflicts concerning the procedure.

Qingming Ni et al. enhanced the fact that emergent cholecystectomy should be performed in patients eligible for surgery as soon as acute cholecystitis is diagnosed, despite recognizing the role of percutaneous drainage in case of deteriorated clinical status[18].

Even though only a minor part of all patients retrospectively reviewed by Pandanaboyana Sanjay et al. underwent later surgery, authors noted higher risk of conversion to open cholecystectomy among patients who had been submitted to percutaneous cholecystostomy[19]. Also, acute cholecystitis recurrence was registered in one in each four patients during study follow-up[19]. The study has also put in evidence the correlation between percutaneous cholecystostomy and high mortality rate due to sepsis at hospital admission, as well as 1-year mortality due to other causes unrelated to cholecystostomy[19].

Mehrdad Nikfarjam et al. additionally observed that a substantial proportion of patients required later surgery, with 9 out of 32 patients undergoing surgery at a median of 73 days since drainage[20]. This particular study also found hypotension and absence of common bile duct filling on initial cholangiography

to be independent prognostic factors, associated with long-term survival reduction[20].

Further prognostic factors were detected by Khang Wen Pang et al.[21]. In fact, authors predicted an increased cholecystitis recurrence risk among patients presenting with higher alkaline phosphatase (ALP) at hospital admission and patients with acute cholecystitis complicated with acute myocardial infarction (AMI). Therefore, investigators state that these specific groups of patients might benefit from definitive cholecystectomy, while taking part in the consensual opinion that surgical profile should persevere as the major predictive factor for clinical decision[21].

## DISCUSSION

Widely recognized Tokyo Guidelines, recently revised in 2013, have recommended emergent percutaneous cholecystostomy and subsequent interval cholecystectomy for cases of severe acute cholecystitis, classified as grade III and moderate cases, or grade II, only for when patients appear to be refractory to conservative treatment[13].

All studies included in this review have recognized a global beneficial use of cholecystostomy in selected patients, particularly among those considered non-eligible for cholecystectomy. Indeed, thorough search has put in evidence an historical belief that correlates populations of an advanced age, in critical clinical condition or with several comorbidities with an inappropriate surgical profile. L.R. Jenkinson et al. have previously associated cholecystectomy performed in an elderly subset of patients with morbidity rates of up to 46% [19],[22]. Further claims have reported surgical procedures in acute settings among high-risk individuals lead to up to 4.5% mortality rates along with 41% morbidity cases mainly due to anaesthetic intercurrences and intrinsic severe comordities[15],[23].

In this demanding clinical context, cholecystostomy emerges as a potentially safe treatment choice for challenging patients, seemingly able to improve both prognosis as a single approach and outcome among cases requiring later cholecystectomy. In fact, symptomatic relief and sepsis treatment have been previously described among 86% of patients submitted to percutaneous drainage [9],[20]. Included in this review, the investigation led by Mehrdad et al. further attest symptomatic treatment and hospital discharge among 91% of patients who underwent cholecystostomy after having been considered unfit for general anaesthesia [20]. As mentioned before, all remaining records included corroborate the advantageous indication for this purpose. Moreover, Byung Hyo Cha et al. obtained successful results when focusing on the role of percutaneous cholecystostomy as definitive management of individuals in critical condition, with no recurrences to register and tubes effectively removed in 75.6% of patients[16].

Despite the optimistic outlook, lengthy database searching for this review has revealed several papers which, despite not qualifying for inclusion criteria and therefore having been excluded, demonstrated conflicting evidence on whether percutaneous cholecystostomy or cholecystectomy should be recommended for better outcomes. A decade long retrospective analysis comprising more than 300 000 patients, conducted in the University of California, San Diego[24], found that patients submitted to cholecystostomy displayed lower risk of procedure-associated complications than patients who underwent surgery; however, mortality was reported to be significantly increased among cholecystostomy patients (odds ratio of 5.2, $p < 0.001$), as well as total hospital length of stay and charges associated. Abi-Haidar et al. have also described not only association of percutaneous cholecystostomy with statistically significant longer hospital length of stay ($p < 0.001$), but also increased complication ($p = 0.01$) and hospital readmission rates ($p = 0.006$) when compared to early cholecystectomy, with 21.4% patients having been eventually readmitted[25]. Researchers add that even laparoscopic cholecystectomy conversion to open procedure, traditionally correlated with quite poor outcome scenarios, showcased better clinical

performance, with decreased number of systemic (25.0% vs 43.1%), hepatobiliary (52.8% vs 68.6%) and other (2.8% vs 7.8%) complications comparing to percutaneous cholecystostomy[25].

Originally, a table comprising results systematically collected from all thirteen articles was created. However, multiple discrepancies were extensively detected as far as study designs were concerned. In fact, articles differed greatly in patient selection for procedure indication criteria, data collected, clinical outcomes sought and follow-up time. This has occasioned hazardous comparison between results found, thereby impairing further statistical analysis and weakening potential conclusions for cholecystostomy validation in acute cholecystitis treatment.

As it has been previously stated in literature[20], only randomized controlled trials may effectively clarify whether percutaneous cholecystostomy should be relied on to achieve safe and successful acute cholecystitis treatment. If so, clinical criteria should be formally established so as patients benefit from this procedure. Dutch CHOCOLATE (percutaneous cholecystostomy versus laparoscopic cholecystectomy) multicentre randomized controlled trial on acute cholecystitis treatment among surgical high-risk populations may provide the awaited evidence based guidelines on the best therapeutic approach[23].

## CONCLUSIONS

All studies included in this review affirm percutaneous cholecystostomy is as a safe procedure with largely successful outcomes when performed in high-risk surgical patients with acute cholecystitis, especially those of an advanced age or who bear significant comorbidities. However, further investigation is needed to strengthen evidence on the role of this procedure.

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# TIROIDITE SUPURATIVA AGUDA

## ACUTE SUPPURATIVE THYROIDITIS

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**RESUMO**

A tiroidite supurativa aguda é uma doença extremamente rara de natureza infecciosa não viral. Na maioria dos casos a infecção é de origem bacteriana. Tradicionalmente, o tratamento tem consistido em antibioterapia dirigida associado a drenagem cirúrgica. Existem, no entanto, relatos recentes de casos submetidos apenas a tratamento conservador. Apresenta-se um caso clínico de tiroidite supurativa aguda num adulto, resolvido com terapêutica não invasiva.

***Palavras-chave:*** *Tiroidite; Supurativa; Bacteriana; Infecciosa.*

**ABSTRACT**

Acute suppurative thyroiditis is an extremely rare non-viral infectious disorder, mostly of bacterial origin. The treatment typically consists of antibiotics and surgical drainage. However, recent reports have suggested that conservative management may suffice in selected cases. We present a case of acute suppurative thyroiditis managed with non-invasive therapy only.

***Key words:*** *Thyroiditis; Suppurative; Bacterial; Infectious.*

## INTRODUÇÃO

Inicialmente descrita por Bauchet em 1857[1], a tiroidite supurativa, infecciosa, bacteriana ou piogénica aguda (TSA) é uma doença rara, de etiologia infecciosa não viral[2] e potencialmente fatal[3]. Globalmente, perfaz apenas 0,1-0,7% de toda a patologia da tiróide[1], mas a sua prevalência tem vindo a aumentar nas últimas décadas, possivelmente devido ao maior número de doentes imunodeprimidos[3].

A TSA ocorre de forma idêntica em ambos os sexos[3] e surge mais frequentemente na população pediátrica (92% dos doentes)[5] devido à maior prevalência de alterações anatómicas predisponentes, em particular, as fístulas do seio piriforme[3]. No adulto o principal mecanismo de infecção é a via hematógena ou linfática a partir de um foco respiratório[4].

Tradicionalmente, o tratamento da TSA tem consistido em cirurgia (drenagem cirúrgica ou tiroidectomia parcial/total) associado a antibioterapia[1].

Contudo, a adopção de métodos de drenagem menos invasivos[2], ou mesmo a antibioterapia isolada, têm sido relatados, recentemente, como métodos terapêuticos igualmente eficazes[1].

A pertinência do caso a seguir relatado prende-se, fundamentalmente, com a invulgaridade da doença em causa e com o sucesso da estratégia terapêutica adoptada.

## DESCRIÇÃO DO CASO

Uma doente de 87 anos é admitida no serviço de urgência (SU) por febre, tremores e dor abdominal com 1 dia de evolução. Como antecedentes referia diabetes não-insulinotratada, bradidisritmia, litíase biliar e hipertensão arterial. A medicação habitual consistia em lansoprazol, gliclazida, furosemida, losartan, digoxina e ácido acetilsalicílico. Não referia alergias medicamentosas.

Ao exame objectivo encontrava-se febril (38,4ºC), eupneica, orientada e hemodinamicamente bem. Na face anterior do pescoço era evidente uma tumefação volumosa, discretamente dolorosa, mas sem outros sinais inflamatórios. A auscultação cardiopulmonar não revelava alterações. A palpação abdominal despertava alguma dor no epigastro, mas sem sinais de irritação peritoneal e sem sinal de Murphy vesicular.

Na avaliação laboratorial destacava-se leucocitose (26200/µL) com neutrofilia (22770/µL), elevação da proteína C reactiva (PCR) – 14,5 mg/dL, bilirrubina total – 2,5 mg/dL e bilirrubina directa – 0,8 mg/dL. Os restantes parâmetros hepáticos e a amilasemia encontravam-se normais.

A avaliação imagiológica consistiu em radiografia de abdómen em pé, que não revelou alterações relevantes, e ecografia abdominal, onde se documentou litíase da vesícula biliar sem alterações evocativas de inflamação vesicular aguda, dilatação das vias biliares ou líquido livre intraperitoneal. A ecografia foi complementada por colangio-ressonância magnética 2 dias após a admissão, que não revelou quaisquer achados adicionais.

Por suspeita de colangite foi proposto internamento e iniciada antibioterapia empírica com piperacilina-tazobactam. No primeiro dia, apesar da melhoria da pirexia e dos sintomas abdominais, constatou-se um agravamento da dor cervical e a instalação de disfagia para líquidos. Apresentava também uma respiração ruidosa, rubor, dor e calor associados à tumefação cervical, previamente inexistentes. Neste contexto, foram efectuadas laringoscopia e ecografia cervical. A primeira revelou apenas alguma desidratação da mucosa orofaríngea e estase salivar. A ecografia evidenciou uma área infiltrativa hipoecogénica dispersa em ambos os lobos da tiroide bem como um nódulo do lobo esquerdo, de contornos bem definidos, com 20mm de maior diâmetro. Foram efectuadas punções aspirativas por agulha fina (AAF) com obtenção de material para exames bacteriológico e citológico. No exame cultural foi isolado um *Streptococcus milleri* sensível à penicilina. O exame citológico revelou-se rico em neutrófilos e linfócitos, compatível com o diagnóstico de tiroidite bacteriana aguda. A avaliação laboratorial da função tiroideia não revelou alterações.

Perante estes resultados, obtidos ao 5º dia de internamento, a antibioterapia foi alterada para penicilina G. Foi também realizada uma tomografia computorizada (TC) cervical que evidenciou densificação e heterogeneidade do tecido adiposo subcutâneo e das fáscias cervicais, associado a aumento das dimensões e heterogeneidade da tiroide (fig. 1). Existiam também múltiplas bolhas gasosas, mas sem colecções líquidas circunscritas. No parênquima pulmonar não se identificaram focos de condensação ou infiltrados intersticiais.

Do ponto de vista evolutivo verificou-se uma melhoria clínica significativa ao fim de 6 dias de terapêutica com penicilina, com resolução da disfagia, da respiração ruidosa e dos sinais inflamatórios cervicais. Laboratorialmente, as bilirrubinas normalizaram, e os parâmetros inflamatórios regrediram significativamente. Manteve, contudo, um bócio volumoso e algum enfisema subcutâneo nos escavados supraclaviculares.

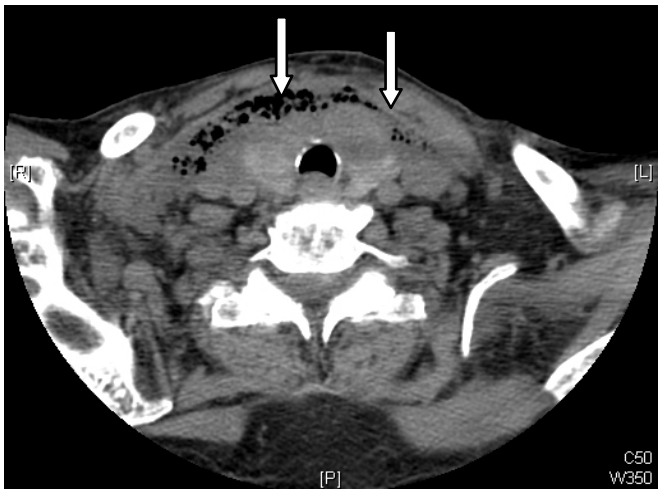


Fig. 1

Por este motivo foi repetida TC que revelou várias colecções líquidas circunscritas laterofaríngeas, retrocricoideias, laterotraqueais e lateroesofágicas (fig. 2), para além das alterações já anteriormente descritas.

Perante este aparente agravamento imagiológico, optou-se por manter a doente internada e prolongar a terapêutica com penicilina G em associação com metronidazol. Ainda assim, e atendendo à boa evolução clínica e laboratorial, optou-se por não drenar as colecções.

Ao 20º dia de tratamento com penicilina (15º de metronidazol) repetiu reavaliação por TC. O exame demonstrou uma melhoria de todas as colecções anteriormente identificadas, bem como dos diversos componentes enfisematosos associados. Teve alta clinicamente bem ao fim de 28 dias de tratamento com penicilina (22 dias de metronidazol), tendo ainda cumprido 2 semanas adicionais de amoxicilina em ambulatório.

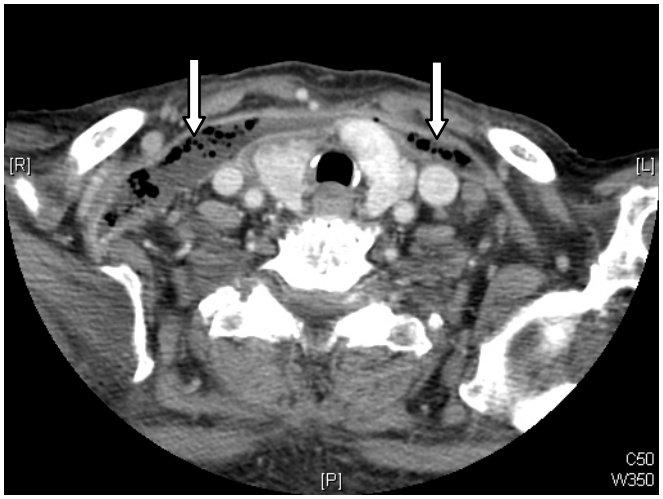


Fig. 2

Ao 3º mês, e já em consulta externa, foi repetida TC cervical que demonstrou reabsorção completa do enfisema, das colecções e dos aspectos infiltrativos previamente descritos, persistindo apenas o carácter nodular da tiroideia. Do ponto de vista clinico e laboratorial a doente permaneceu sempre eutiroideia e sem quaisquer sequelas. Actualmente encontra-se sob vigilância clínica na consulta.

## DISCUSSÃO

A tiróide é uma glândula extremamente resistente à infecção[2]. Esta característica tem sido atribuída à sua extensa vascularização e drenagem linfática, elevadas concentrações tecidulares de iodo, produção local de peróxido de hidrogénio, revestimento capsular e localização anatómica[2].

No adulto a infecção surge, geralmente, na presença de bócio multinodular[4]. Regra geral, o agente microbiano alcança a glândula por via hemática ou linfática a partir de um foco respiratório ou, no caso da criança, a partir de uma fístula do seio piriforme. Estão também descritos casos de TSA por persistência do canal tiroglosso, por contiguidade (perfurações do esófago, traumatismos ou neoplasias) ou por complicações de procedimentos invasivos/cirúrgicos cervicais[3]. A infecção VIH e a diabetes mellitus são também factores de risco importantes[4].

No caso aqui relatado, e apesar dos exames realizados, nunca se chegou a apurar o foco etiopatogénico. Mesmo atendendo ao facto de a doente ter sido admitida, inicialmente, por um quadro suspeito de colangite, este nunca chegou a confirmar-se. Por outro lado, os resultados da laringoscopia e da TC tornaram mais remotas as hipóteses de fístula do seio piriforme ou de perfuração

do esófago cervical como ponto de partida para a infecção.

Os agentes infecciosos mais frequentemente implicados na TSA compreendem, por ordem de frequência, as bactérias aeróbias Gram-positivas dos géneros *Staphylococcus* e *Streptococcus*, os aeróbios Gram-negativos, os anaeróbios e, em situações mais raras, os fungos e parasitas[1].

O sintoma dominante na apresentação é a dor na região tiroideia, à qual se associa aumento do volume glandular, rubor, calor e dor à palpação[2]. A febre e a odinofagia são também sintomas frequentes e, em casos raros, pode também haver lugar à formação de enfisema tecidular[2].

Laboratorialmente, observa-se elevação dos parâmetros inflamatórios[4]. O estudo da função tiroideia deve ser efectuado, pois, em casos raros, pode surgir tirotoxicose secundária à destruição folicular com consequente libertação de hormonas tiroideias[1]. A utilidade do doseamento da tiroglobulina (Tg) é questionável uma vez que apenas remete para inflamação tiroideia e não sugere qualquer etiologia[1].

A ecografia pode ser adoptada como exame imagiológico inicial[3]. Permite não apenas a identificação de colecções intra ou extra-tiroideias[5], mas também a realização de punções AAF[3] e a realização de drenagens ecoguiadas[1]. Contudo, na maioria dos centros a TC com contraste endovenoso é considerada o exame de primeira linha, permitindo uma melhor avaliação anatómica, com destaque para a extensão cervical ou mediastínica dos abcessos, e, por vezes, a identificação de uma fístula do seio piriforme[1]. A videolaringoscopia, eventualmente complementada com técnicas de insuflação do seio piriforme ou de injecção de contraste nos casos duvidosos, deve também ser realizada para excluir fístula do seio piriforme[5]. No caso particular desta doente a melhoria clínica constatada aliada à idade avançada, levou-nos a optar por não prosseguir com estudos etiológicos invasivos adicionais.

O principal diagnóstico diferencial na TSA coloca-se com tiroidite subaguda, doença de etiologia viral, autolimitada e que causa frequentemente tirotoxicose (contrariamente à TSA que cursa, geralmente, em eutiroidismo)[2]. A punção AAF é o exame *gold strandard* que permite a distinção citológica entre ambas[2], para além da exclusão de neoplasia subjacente[4] e do isolamento do agente microbiano implicado[4].

O tratamento da TSA consiste em antibioterapia de largo espectro e drenagem de eventuais abcessos[4]. A antibioterapia deve ser mantida durante pelo menos 14 dias ou até à resolução clínica completa[1]. A drenagem urgente (percutânea ou cirúrgica) está recomendada na obstrução da via aérea[1]. No doente estável e sem compromisso da via aérea a drenagem ecoguiada por AAF pode ser suficiente[1].

A tiroidectomia urgente só deve ser equacionada na falência da abordagem inicial com drenagem e antibioterapia[1]. A ressecção diferida está recomendada quando ocorre necrose extensa da glândula ou na suspeita de neoplasia[1].

Na presença de fístula do seio piriforme a ablação cirúrgica ou por quimiocauterização laringoscópica deve ser realizada após resolução da infecção, de forma a prevenir a recorrência[3].

Recentemente, alguns centros têm vindo a adoptar, com sucesso, estratégias terapêuticas menos invasivas[1]. No caso aqui relatado, foi possível resolver a infecção com antibioterapia isolada sem necessidade de drenagem. Optou-se também por não propor tiroidectomia dada a inexistência de alterações anatómicas predisponentes documentadas, achados citológicos suspeitos, idade avançada e resolução clinico-imagiológica completa sem sequelas.

## CONCLUSÃO

A TSA é uma doença infecciosa rara mas potencialmente fatal se não for diagnosticada e tratada precocemente. No adulto a causa mais frequente é a disseminação bacteriana hematógena com origem noutro foco infeccioso. O tratamento assenta na antibioterapia de largo espectro e drenagem do(s) abcesso(s) eventualmente presentes.

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# TRATAMENTO CIRÚRGICO DO TUMOR DO CORPO CAROTÍDEO

## SURGICAL TREATMENT OF CAROTID BODY TUMORS

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**RESUMO**

Os paragangliomas são tumores raros que se desenvolvem a partir do tecido paraganglionico. Na cabeça e pescoço, os seus principais locais de crescimento são o corpo carotídeo localizado na bifurcação da artéria carótida comum, o *foramen jugulare*, o ouvido médio e a porção cervical do nervo vago. Os autores relatam o caso clínico de uma doente portadora da mutação do gene SDHB com um tumor do corpo carotídeo do tipo II de Shamblin. O tratamento cirúrgico destes tumores é complexo e o seu seguimento deverá ser realizado em centros com experiência.

***Palavras-chave:*** *Paraganglioma; Tumor do corpo carotídeo; Tratamento; Resseção cirúrgica; Classificação de Shamblin.*

**ABSTRACT**

Paragangliomas are rare tumors that develop from paraganglionic tissue. In head and neck, its main growth sites are the carotid body located at the bifurcation of the common carotid artery, the *foramen jugulare*, the middle ear and the cervical portion of the vagus nerve. The authors report the case of a holder of a SDHB gene mutation with a carotid body tumor Shamblin type II. Surgical treatment of these tumors is complex and its follow-up should be performed in centers with experience.

***Keywords (MeSH Medical Subject Headings, Index Medicus):*** *Paraganglioma; Carotid body tumor; Treatment; Surgical resection; Shamblin classification.*

## INTRODUÇÃO

Os paragangliomas constituem uma pequena percentagem de todas as neoplasias da região da cabeça e pescoço. No entanto, é nesta topografia que o desenvolvimento destes raros tumores neuroendócrinos é mais comum.[1]

A maior parte dos paragangliomas da cabeça e pescoço são lesões benignas que se desenvolvem a partir do tecido paragangliónico das artérias ou nervos cranianos, o qual tem origem na crista neural.[1] Os seus principais locais de crescimento são a bifurcação da artéria carótida comum, o *foramen jugulare*, o ouvido médio e a porção cervical do nervo vago.[2]

O corpo carotídeo, descrito por Albrecht Von Haller em 1743, localiza-se no tecido peri-adventício da bifurcação da artéria carótida comum e funciona como um quimiorrecetor para a modulação do desempenho imunológico e cardiorrespiratório.[3] Os tumores do corpo carotídeo (TCC) constituem os paragangliomas mais comuns da cabeça e pescoço.[1]

Na nossa Instituição foram operados 21 TCC nos últimos 14 anos (de 2006 a 2019).

## CASO CLÍNICO

Doente do sexo feminino, com 38 anos e sem antecedentes pessoais relevantes, que recorreu ao Serviço de Urgência do Hospital da sua área de residência, referenciada pelo médico assistente por uma massa cervical à esquerda, com aumento recente do tamanho.

A doente encontrava-se assintomática e ao exame objetivo apresentava uma tumefação palpável latero-cervical à esquerda, não pulsátil, com cerca de 5 cm de maior diâmetro. Não apresentava adenopatias cervicais ou nódulos tiroideus palpáveis, assim como lesões cutâneas ou da mucosa da cavidade oral suspeitas. Encontrava-se normocárdica e normotensa.

Realizou uma ecografia cervical que demonstrou uma imagem nodular heterogénea em topografia jugulo-carotídea esquerda, com 5 cm de maior diâmetro e posteriormente uma Tomografia Computorizada que revelou tratar-se de uma lesão hipercaptante em fase arterial, compatível com tumor do corpo carotídeo – Fig. 1 A.

Foi referenciada à nossa Instituição, onde realizou como estudo complementar uma Angiorressonância Magnética que confirmou a presença de uma lesão expansiva bem circunscrita no espaço carotídeo infra-hioideu esquerdo, centrada na bifurcação da artéria carótida comum, determinando afastamento dos ramos interno e externo. O estudo angiográfico permitiu definir a sua vascularização predominante pela artéria faríngea ascendente esquerda. – Fig. 1 B.

O doseamento das aminas biogénicas não revelou alterações.

A Tomografia Computorizada toraco-abdominal não revelou a presença de lesões suspeitas de metástases.

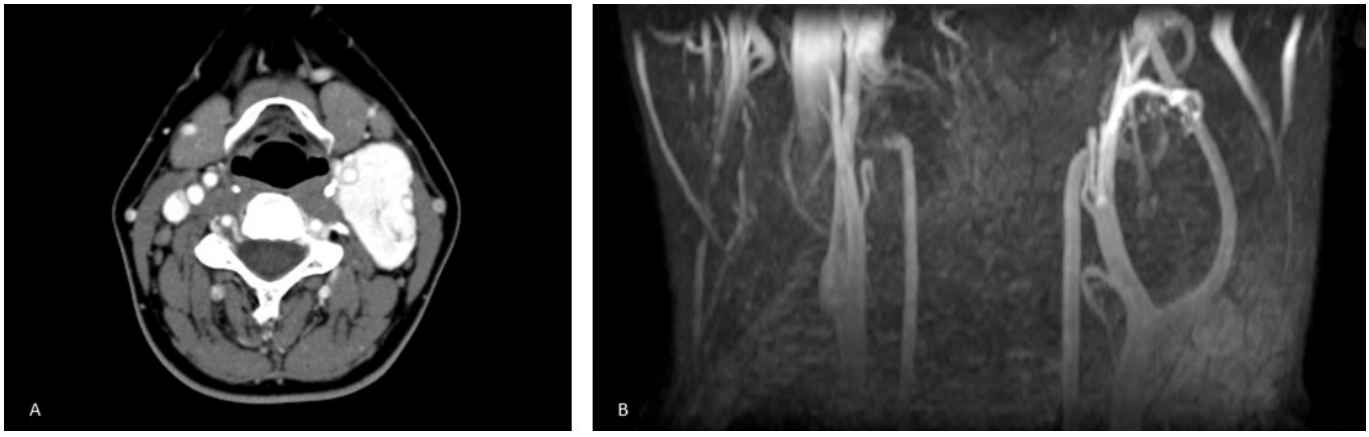


Fig. 1 A. **Imagem da Tomografia Computorizada, corte axial, em fase arterial.** B. **Estudo angiográfico, Angioressonância Magnética.**

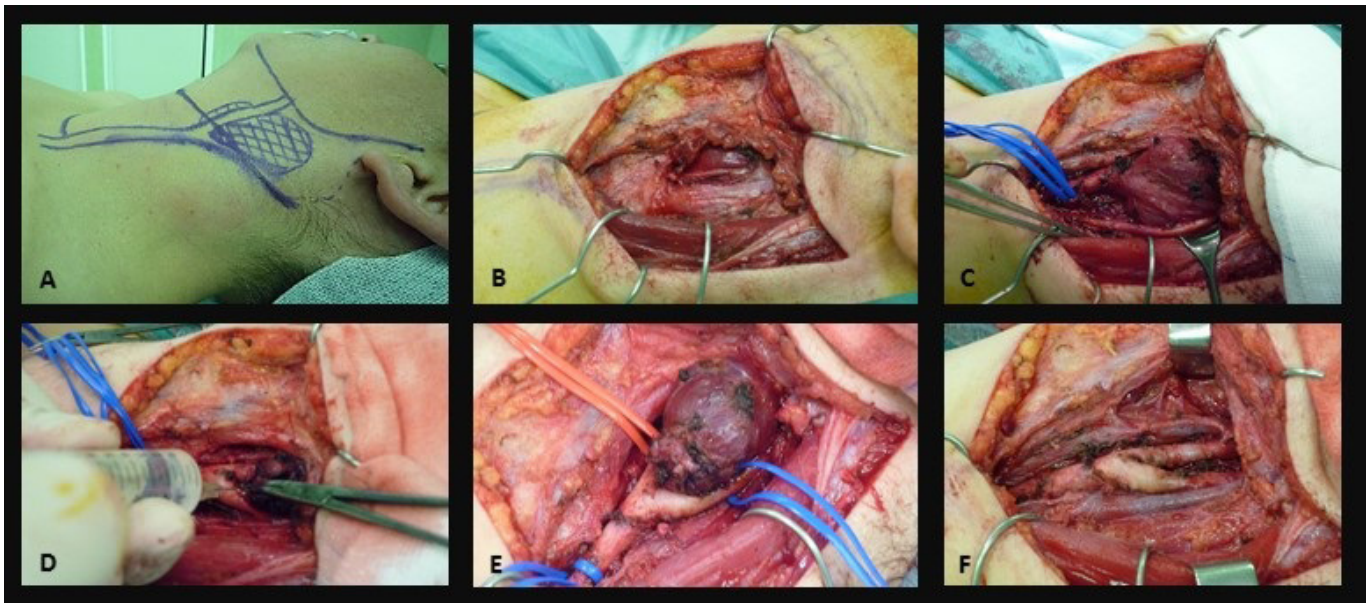


Fig. 2 A. **Esquema de superfície;** B. **Nódulos linfáticos hiperplásicos localizados sobre o tumor;** C. **Identificação do tumor e das artérias carótidas;** D. **Injeção de lidocaína peri-tumoral;** E. **Isolamento do tumor do corpo carotídeo e a sua relação com as artérias carótida comum, interna e externa – tumor do tipo II de Shamblin;** F. **Leito tumoral.**

A doente foi então submetida a exérese do tumor do corpo carotídeo – Fig. 2.

O pós-operatório decorreu sem complicações.

A histologia confirmou tratar-se de um paraganglioma do corpo carotídeo, demonstrando o estudo imunohistoquímico positividade para cromogranina, sinaptofisina e PS100.

O estudo genético efetuado revelou que a doente era portadora da mutação do gene SDHB.

A doente mantém-se em seguimento na consulta externa da nossa Instituição, encontrando-se assintomática, sem déficits neurológicos ou vasculares, sem sinais de recidiva local ou sistémica e sem identificação de novos paragangliomas.

## DISCUSSÃO

### Etiologia

A hipoxémia crónica (sustentada ou intermitente) estimula a hipertrofia e hiperplasia do corpo carotídeo. Os TCC que se formam somente pela hipoxémia crónica, são denominados não-hereditários ou esporádicos.[3]

Os tumores familiares constituem aproximadamente 10 % de todos os tumores. Possuem um modo de transmissão autossómica dominante com penetrância incompleta e são caracterizados por uma grande incidência de tumores bilaterais ou multicêntricos.[3]

As mutações implicadas nas formas familiares dos TCC são mutações do gene SDH (succinato desidrogenase). Este gene codifica três sub-unidades (B, C e D) do complexo mitocondrial II, um complexo heterotetramérico envolvido no ciclo de Krebs e na cadeia aeróbica de transporte de eletrões.[5]

Quando os TCC estão associados a estas mutações, verifica-se frequentemente a existência de outros paragangliomas silenciosos.[5]

Algumas lesões surgem em pacientes com síndromes genéticos como o Síndrome de Von-Hippel-Lindau, o MEN (Multiple endocrine neoplasia) tipo 2 ou a Neurofibromatose tipo I.[4]

### Diagnóstico

A maior parte dos pacientes com TCC são assintomáticos. A principal queixa referida é a presença de uma massa cervical, muitas vezes pulsátil

e demonstrando mobilidade medial e lateralmente, sendo fixa superior e inferiormente – Sinal de Fontaine.[3] Se o TCC é funcionante (o que é raro), poderá apresentar-se com palpitações, rubor facial, taquicardia e hipertensão arterial, acompanhado de elevação do nível de catecolaminas no sangue.[2] Pode ainda haver paralisia de um nervo craniano que esteja envolvido pelo tumor.

A angiografia constituía o exame de eleição no diagnóstico dos TCC. No entanto, o risco de complicações neurológicas fez com que a sua utilização esteja agora reservada para a embolização tumoral pré-operatória, que deverá ser realizada idealmente dentro das 48h anteriores à cirurgia, de forma a evitar a formação de circulação colateral e minimizar a resposta inflamatória local.[2] A maior parte do suprimento vascular do TCC parte da artéria carótida externa, pelo que a embolização seletiva por angiografia poderá facilitar a excisão tumoral com uma menor hemorragia. No entanto, Jae-Yol Lim *et al*[2] demonstraram não haver diferença significativa nem na hemorragia operatória nem no tempo cirúrgico entre os doentes que foram submetidos a embolização e os que não foram.

A Tomografia Computorizada (TC) com contraste endovenoso permite o diagnóstico correto dos TCC. Sendo estes tumores lesões altamente vasculares, revelam-se na TC como lesões hipercaptantes em fase arterial e que separam a artéria carótida interna da artéria carótida externa – sinal de Lyre.

A Ressonância Magnética aumentou ainda mais a capacidade de um diagnóstico correto através da captação de imagens ponderadas em T2 com a utilização de contraste de gadolíneo. Os TCC revelam-se como uma lesão hiperintensa na ponderacão T2, isointensa face ao tecido muscular em T1, revelando realce precoce e intenso após administracão de contraste.

Para além disso, a Angioressonância magnética constitui um exame complementar de diagnóstico não invasivo e que demonstra facilmente a relação do tumor com as artérias carótidas, permitindo um planeamento cirúrgico mais adequado.

A utilização da PET Gálio 68-DOTA-NOC tem demonstrado vantagem no diagnóstico e seguimento de alguns tumores neuro-endócrinos, sendo uma modalidade não invasiva importante na deteção, caracterização e seguimento dos TCC.[4]

A Classificação de Shamblin divide os TCC em três categorias, baseando-se na relação do tumor com as artérias carótidas e nervos cranianos.

Nos tumores do tipo I, as artérias estão apenas separadas pelo tumor. No tipo II de Shamblin, o tumor é indentado pelas artérias carótidas, havendo uma goteira profunda no tumor provocada pelas mesmas. Neste tipo, os nervos hipoglosso e laríngeo superior localizam-se na superfície tumoral. Finalmente, no tipo III de Shamblin, as artérias e os nervos estão completamente envolvidos pelo tumor.

A Classificação de Shamblin poderá ser utilizada para estimar a taxa de complicações neurovasculares pos-operatórias. Há ainda uma relação entre a mesma e a hemorragia operatória. Tumores Shamblin tipo III implicam uma hemorragia operatória duas vezes superior aos tumores Shamblin tipo I ou II.[2]

Histologicamente é difícil a diferenciação entre os paragangliomas benignos ou malignos. A presença de metastização ganglionar ou à distância (em 5 – 10% dos casos) faz o diagnóstico de malignidade.[1] No entanto, o diagnóstico das metástases pode ser realizado décadas após o aparecimento do tumor primário. As metástases do TCC localizam-se mais frequentemente no osso, no fígado e no pulmão.[4] A evidência de invasão local com paralisia de um nervo craniano ou infiltração das estruturas adjacentes aumenta também a suspeita de malignidade.[1]

## Tratamento

Uma vez que o tratamento cirúrgico dos tumores do corpo carotídeo, quando realizado em centros com experiência, geralmente não causa dano neurológico, a maioria destes doentes com tumores até 6-7 cm

e sem extensão para a base do crânio, é tratada cirurgicamente. [1]

No entanto, a indicação cirúrgica depende dos sintomas do paciente, do tamanho da lesão, da multiplicidade das lesões, do risco cirúrgico do doente e do risco de uma lesão neurológica durante a cirurgia.[1] Quando a morbilidade decorrente da cirurgia poderá ser maior do que os efeitos deletérios do crescimento natural destes tumores, uma vez que estes tumores têm um crescimento muito lento (1-2 mm por ano, em média), estes doentes podem ser acompanhados segundo a filosofia do "*watch and wait*", quando assintomáticos e com baixo risco de malignidade. [1]

Antes do tratamento cirúrgico, em lesões de grandes dimensões, deverá ser considerada a necessidade de avaliação do *crossover* da circulação intracraniana (com avaliação da artéria carótida interna contra-lateral e das artérias vertebrais) de modo a calcular o risco de défices neuro-vasculares, caso seja necessária a laqueação da artéria carótida interna durante a cirurgia.

A dissecção tumoral deverá ser peri-adventícia e após realizado o controlo proximal e distal das artérias e dado que a maior parte da vascularização tumoral provém da artéria carótida externa, deverá ser feita a laqueação precoce dos vasos provenientes da mesma, de forma a facilitar a resseção cirúrgica.[2] A artéria faríngea ascendente é muitas vezes a artéria responsável pela maior parte da vascularização tumoral.[2]

Recentemente, Van der Borgt *et al* propuseram uma dissecção crânio-caudal (em alternativa à clássica abordagem caudal-cranial). Segundo estes autores, esta abordagem ao laquear inicialmente a artéria faríngea ascendente e os outros vasos provenientes da artéria carótida externa, facilita um controlo precoce de todos os nervos envolventes (pares cranianos X, XII e ramo mandibular do nervo facial) minimizando a morbilidade pos-operatória.[6]

Durante o curso da dissecção, podem ocorrer bradicardia e hipotensão como resultado da estimulação dos barorreceptores na bifurcação carotídea. A infiltração de lidocaína a 1% no plano sub-adventício do bulbo carotídeo reverterá imediatamente o quadro. [1]

Quando é necessário a excisão parcial da artéria carótida, a reconstrução poderá ser feita utilizando a veia safena, a artéria ou veia femural ou uma prótese vascular.[3]

Apesar dos avanços na técnica cirúrgica, a incidência de complicações neuro-vasculares peri-operatórias, especialmente défices de nervos cranianos e hemorragia intraoperatória, não é negligenciável.[3]

Os paragangliomas são radiossensíveis, pelo que a radioterapia poderá ser uma alternativa de tratamento nos pacientes que não podem ser submetidos a tratamento cirúrgico, de forma a estabilizar ou reduzir o TCC. [3]

Quando se verifica o aparecimento de metástases, o tratamento de primeira linha é a cirurgia.[3] Nos casos em que não é possível ressecar cirurgicamente o tumor primário e metástases, é possível utilizar esquemas de poliquimioterapia (com agentes como a Ciclofosfamida, Doxorrubicina e Cisplatina) assim como recorrer à utilização de análogos da somatostatina ou à terapêutica com radionuclídeos – "Peptide receptor radionuclide therapy" (PRRT) – nos tumores com expressão de recetores de somatostatina. [1, 7]

## Seguimento

Deve ser pesquisada a existência de mutações do gene SDH em todos os doentes com TCC pois a estratégia de *follow-up* poderá ser alterada. Enquanto os doentes que não têm mutação requerem apenas uma ecografia anual de controlo, os portadores de mutação e os seus familiares com mutação deverão realizar adicionalmente ressonância magnética da cabeça e pescoço, tórax, abdómen e pélvis ou PET Gálio 68-DOTA-NOC.

## CONSIDERAÇÕES FINAIS

A raridade da entidade, a complexidade do tratamento e a especificidade do seguimento aconselham a que os doentes com TCC sejam referenciados a instituições experientes e polivalentes, de forma a maximizar recursos e minimizar os potenciais efeitos deletérios do tratamento.

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# PORTAL VEIN CROSSING UP IN FRONT OF THE HEPATIC ARTERY

## VEIA PORTA CRUZA A ARTÉRIA HEPÁTICA PELA FRENTE

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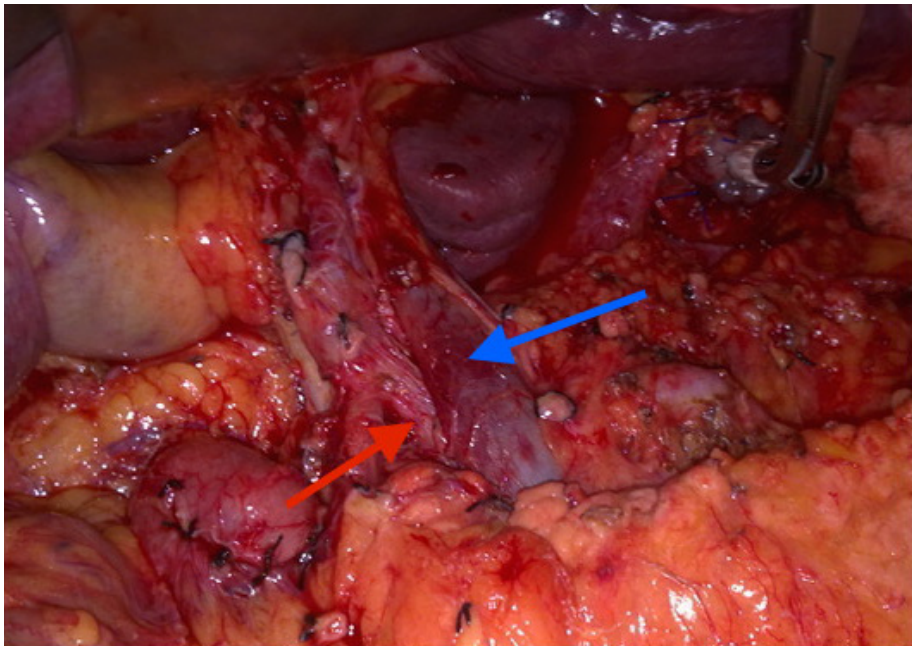
An anatomic rare variation disclosed during a D2 dissection and total gastrectomy for gastric cancer.



LEGEND: **red arrow – hepatic artery; blue arrow – portal vein.**

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# LINFADENECTOMIA TORÁCICA SUPERIOR NO CARCINOMA DO ESÓFAGO

## UPPER THORACIC FIELD LYMPHADENECTOMY FOR OESOPHAGEAL CARCINOMA

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[1] Cirurgia geral IPOLFG

https://www.youtube.com/watch?v=mxbw0HBHp24

A neoplasia do esófago é a sexta causa de morte neoplásica a nível mundial e a sua incidência tem vindo a aumentar. A cirurgia com correspondente linfadenectomia é o único tratamento com intenção curativa.

A linfadenectomia mediastínica superior aborda os gânglios do grupo 105, 106 recR e L, 106 tbR e tbL e 106 pre. A linfadenectomia destes territórios está indicada para tumores situados tanto a nível do terço superior como médio como inferior do esófago torácico.

É importante a sistematização das indicações e da técnica cirúrgica adequada para abordagem deste território.

Este vídeo mostra, de forma sistematizada, a linfadenectomia torácica superior, via aberta, realçando as indicações, a anatomia desta zona e a forma de realizar esta linfadenectomia com a menor morbilidade possível.

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# ENUCLEAÇÃO DE LIPOMA ESOFÁGICO SUBMUCOSO POR VATS

## THORACOSCOPIC ENUCLEATION OF A SUBMUCOSAL ESOPHAGEAL LIPOMA

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https://www.youtube.com/watch?v=Q_PiRipSnIU

**Objetivos:** relato de um caso de uma enucleação toracoscópica de um lipoma esofágico. Os lipomas do trato gastrointestinal, e concretamente os lipomas esofágicos, são extremamente raros. A enucleação cirúrgica está indicada nos casos sintomáticos ou com diagnóstico inconclusivo. Nos últimos anos, a enucleação toracoscópica tem-se vindo a demonstrar como a abordagem preferida para a maioria destas lesões.

**Métodos:** os dados clínicos foram coletados a partir de registos computadorizados do processo do paciente, assim como registos, vídeos e fotografias colhidos durante a cirurgia.

**Resultados:** paciente de 68 anos de idade, sexo masculino, diabético e hipertenso, com clínica de

**Aims:** case-report of a toracoscopic enucleation of esophageal lipoma. Lipomas of the gastrointestinal tract are rare, and those of the esophagus are extremely rare. Surgical enucleation is indicated in case of symptoms or an unclear diagnosis. Toracoscopic enucleation has been developed as a preferred approach for most lesions in recent years.

**Methods:** clinical data collected from computerized records of the patient process and records, video and photography from surgery. Literature review about this subject, using Pubmed search platform.

**Results:** The patient is a 68 years old man, diabetic and hypertensive, presented with dysphagia associated

disfagia, associada a impactação por compressão extrínseca. A endoscopia digestiva alta revelou uma massa no espaço submucoso, com mucosa esofágica normal, a 22cm da arcada dentária superior. A TC revelou um lipoma esofágico de 42x9x16 a nível do esófago medio-superior, com efeito de massa e compressão luminal. Em abril de 2016, o paciente foi submetido a uma enucleação do lipoma esofágico por via toracoscópica vídeo assistida. Foi realizada incisão na camada muscular externa do esófago de forma a expor a lesão, que foi completamente enucleada. A cirurgia e o período pós-operatório decorreram sem intercorrências, tendo alta ao 3º dia. A histologia confirmou o diagnóstico de lipoma. Atualmente, o paciente encontra-se assintomático.

**Conclusões:** os tumores benignos do esófago são muito raros. O tratamento depende da clínica, do tamanho e da origem dos mesmos. Embora os lipomas sejam raros no esófago, o diagnóstico precoce e a ressecção devem ser recomendados para todos os casos sintomáticos. A enucleação VATS de lipomas esofágicos é um tratamento seguro e eficaz.

with extrinsic compression impactation. Upper gastrointestinal endoscopy revealed a submucosal space-occupying mass, with normal mucosa, at 22cm from upper dental arch. CT revealed an upper-medium 42x9x16 esophageal lipoma, with mass effect and luminal narrowing. In April 2016, the patient was submitted to a toracoscopic enucleation of the esophageal lipoma. The tumor location was identified, and the overlying muscle layer of the esophagus was incised to expose the tumor, which was completely enucleated. The surgery and post-operative period was uneventful. Histology confirmed the diagnosis of lipoma, comprising a collection of mature adipose tissue. The patient is currently asymptomatic.

**Conclusions:** benign tumors of the esophagus are very rare. The treatment of suspected esophageal lipoma depends on tumor size and origin. Toracoscopic enucleation of esophageal lipomas is a safe, minimally invasive, and effective treatment. Although lipomas are rare in the esophagus, early diagnosis and resection should be recommended for all symptomatic cases.

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