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Innovations in Radiation Oncology

Radiation therapy is one of the three pillars in the fight against cancer. Over the past decades, there have been significant technological innovations and cutting-edge research in radiation oncology. Major advances have been made especially in three scientific fields: biological science, physics, and clinical applications.

Since the detection of x-rays by Wilhelm Conrad Röntgen in 1895 and their first clinical application in 1896, our biological understanding of how radiation successfully kills cancer cells and of how malignant cells escape cancer treatment has rapidly grown. Due to the early discovery that radiation mainly targets DNA, multifraction regimens have become the gold standard in clinical radiation oncology over the last decades: dividing a dose into a number of fractions has proven to sparse the normal tissue because of sublethal damage repair between the treatment fractions, with regeneration of normal tissue. At the same time, a fractionated treatment regimen increases damage to the tumour because of reoxygenation and synchronizing tumour cells into a radiosensitive phase of the cell cycle. This effect can be further enhanced by adding systemic therapy to the treatment regimen, which became standard for many solid tumours. However, this iconical dogma has been challenged in recent years by cutting-edge research in biology, physics, and clinics.

Application of radiation treatment has been revolutionized by sophisticated technologies, which allow to tailor the radiation dose to the tumour, while minimizing the radiation to organs at risk and otherwise healthy structures (e.g. intensity modulated radiation therapy, volumetric-modulated arc therapy, stereotactic radiation therapy). The computer-controlled shaping of the radiation field (multileaf collimators) permits not only conformation of the radiation fields to the target volume but also modulates the beam intensity pattern across the field. Furthermore, by performing a 4-dimensional CT (3-dimensional anatomy of a patient observed over time) and using markers or transponders the movement of a target (tumours as well as organs at risk) can be easily tracked during each treatment session leading to a high-precision delivery of radiation therapy. One promising approach of how these technical innovations currently are implemented into clinical application are discussed in this issue of the Krebsbulletin by Schröder and Guckenberger in the context of oligometastatic cancer disease.

Beside technological improvements, recent radiobiological discoveries are a key step towards a more personalized cancer treatment in radiation oncology. Novel molecular targets to selectively enhance the effect of radiation to the tumour or to protect the normal tissue are dominating this field, drugs aiming for example at DNA damage and repair, growth receptors, or microvessels. One of the new avenues in this field is discussed by Herrera et al. focusing on the importance of the immune system in tumors as a response to radiation therapy. However, well-designed clinical trials are needed to answer the question if radiation is a critical component to immunotherapy.

Organ preservation has been a major concern of modern cancer treatment for several decades. With decreasing side effects, the previously described sophisticated use of innovative radiation techniques has allowed a more effective organ-preservation therapy to compete successfully with radical surgery in a variety of anatomical sites. Head and neck cancer is one example of the success of combined radiation and chemotherapy. Another story of success is the integral role of radiation therapy in the treatment of breast cancer as presented in the article by Zimmermann. A systematic review on relevant clinical trials on radiation therapy in breast cancer are presented as well as the role of hypofractionation and dose escalation discussed.

In summary, radiation oncologists live in a very exciting time. Our discipline continues to advance at a rapid pace based on innovative developments in biology, physics and clinics. Since the management of cancer patients is multidisciplinary and the medical and technical development is rising rapidly in all medical fields, well-designed clinical trials addressing relevant questions with high ethical and quality standards are needed to validate which of the novel developments are ultimately of benefit to our patients, as highlighted by Datta et al.

Shall this collection of highly interesting articles of the current issue be a source of education and pleasure and hopefully also a source of new ideas for future research in a fascinating medical field!

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Die Pflegeinitiative spaltet die Branche

Die Promotoren des Volksbegehrens sind mit dem Vorwurf des einseitigen Lobbyings konfrontiert.

Im Volk ist die Unterstützung für die Pflegeinitiative gross: Nur acht Monate dauerte es, bis 120 000 Unterschriften für das Begehren, das unter anderem eine Besserstellung der Pflege verlangt, zusammen waren. Doch innerhalb der Branche kann von Einmütigkeit keine Rede sein. In einem NZZ-Gastkommentar hat Pflegefachmann Markus Stadler den «gewerkschaftlichen Röhrenblick» kritisiert, welcher der Initiative anhafte und dem Gesundheitswesen schade. Stadler ist nicht irgendwer: Er hatte gewissermassen den Anstoss für den politischen Prozess gegeben, der letztlich zur Initiative führte. Stadler ging vor einigen Jahren auf den damaligen SVP-Nationalrat Rudolf Joder zu, weil er eine Stärkung der Pflege erreichen wollte. In der Folge arbeitete Joder eine parlamentarische Initiative aus. Weil der Vorstoss im Parlament durchfiel, reagierte der Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner (SBK) Anfang 2017 mit der Lancierung der Initiative.

Dabei sei alles ein wenig aus dem Ruder gelaufen, schreibt Stadler nun: Die heutige interdisziplinäre und vernetzte Sicht im Gesundheitswesen werde von den Initianten ausgeblendet. Stadler erinnert daran, dass in den verschiedenen Bereichen Spitex, Langzeitpflege, Rehabilitation, Akutspital und Ambulatorien keineswegs nur Pflegefachleute eingesetzt werden. In den letzten Jahren gab es einen starken Zuwachs bei den Fachfrauen und Fachmännern Gesundheit (FaGe), die eine dreijährige, weniger anspruchsvolle Berufslehre absolvieren.

Stadler spricht von einer «Alleinstellungsinitiative» der Pflegefachpersonen; der Initiative fehle die systemische Gesamtsicht. Denselben Vorwurf äusserten im vergangenen November auch der Spitalverband H+, Spitex Schweiz und der Heimverband Curaviva: Dass die Volksinitiative den Fokus einseitig auf die «klassische» Diplompflege lege, sei nicht sinnvoll. Ein Dorn im Auge ist den Kritikern folgende Passage im Verfassungstext: Bund und Kantone sollen sicherstellen, «dass eine genügende Anzahl diplomierter Pflegefachpersonen für den zunehmenden Bedarf zur Verfügung steht».

SBK-Präsidentin Helena Zaugg wehrt sich gegen den Vorwurf des einseitigen Lobbyings durch ihren Verband. Sie verweist auf weitere Artikel des Verfassungstexts, in denen von der Pflege allgemein die Rede sei – und damit klar sämtliche beteiligten Berufsgattungen gemeint seien. So fordert die Initiative anforderungsgerechte Arbeitsbedingungen und Möglichkeiten der beruflichen Entwicklung für «die in der Pflege tätigen Personen».

Doch wieso braucht es dann den Artikel, der explizit die Rolle der Pflegefachpersonen herausstreicht? «Wir machen uns Sorgen um die Behandlung und Sicherheit der Patienten, wenn es immer weniger der bestausgebildeten Pflegenden gibt», antwortet Zaugg. Statt der 6000 benötigten werden derzeit bloss 2500 diplomierte Pflegefachleute ausgebildet. Es könne keine Lösung sein, immer mehr Pflegepersonal im Ausland zu rekrutieren, betont Zaugg. Konkret fordert sie, dass beispielsweise die FaGe ein höheres Salär erhalten, wenn sie sich zwei Jahre lang an einer höheren Fachschule zur Pflegefachperson weiterbilden. Der jetzige Ausbildungslohn von nur rund 1000 Franken im Monat schrecke zu viele junge Leute ab – zumal sie nach erfolgter Ausbildung nicht viel mehr verdienen würden denn als FaGe.

Die Initiative sieht zudem vor, dass Pflegefachleute künftig in Eigenregie Leistungen erbringen und diese direkt über die Krankenkasse abrechnen dürfen. Hinter dieser Kernforderung stehen sowohl Markus Stadler als auch die Verbände H+, Spitex Schweiz und Curaviva. Nachdem der Bundesrat es Anfang März abgelehnt hat, den Initianten mit einem direkten Gegenvorschlag auf Verfassungsstufe entgegenzukommen, liegt der Ball nun beim Parlament. Gesundheitspolitiker von SP, CVP und FDP sind laut «Tages-Anzeiger» offen für einen indirekten Gegenvorschlag auf Gesetzesstufe. Als Basis könnte der einst versenkte Vorstoss von Rudolf Joder dienen.

Die Kassen warnen zwar vor einer Mengenausweitung und Mehrkosten, wenn die Pflegenden in eigener Verantwortung Pflegeleistungen bei der Spitex oder in Heimen erbringen dürfen. Doch es gibt auch berechtigte Hoffnungen, dass das Gegenteil der Fall wäre: Wenn der Arzt nicht jedes Mal pflegerische Leistungen anordnen müsste, könnte dies Zeit und Geld sparen. Sollte eine Gesetzesreform ihren Forderungen weitgehend entsprechen, wären die Initianten bereit, das Volksbegehren zurückzuziehen. Mit der Initiative haben sie ein starkes Druckmittel in der Hand – denn die Chancen auf ein Volks-Ja sind mehr als intakt.

Neue Zürcher Zeitung, 28.03.2018

Radikales Mittel gegen teure Medikamente

Public Eye und die Krebsliga warnen vor zu teuren Arzneien – etwa gegen Brustkrebs – und schlagen drastische Massnahmen vor. Therapien für über 100 000 Franken pro Jahr würden das Gesundheitssystem bedrohen. Auch die Kosten verlangen Reformen.

Was darf es kosten, damit ein Krebskranker ein Jahr länger lebt? Eine heikle Frage, aber angesichts von Therapiekosten von 100 000 Franken und mehr pro Jahr schlagen die Nichtregierungsorganisation Public Eye und die Schweizer Krebsliga Alarm. «Von 2007 bis 2016 sind die Kosten für Krebsmedikamente um 184 Prozent gestiegen», rechnet Public Eye in einem neuen Bericht vor. «Die aktuellen Preise neuer Krebsmittel sind nicht länger akzeptabel», sagt auch Thomas Cerny, Präsident der Krebsforschung Schweiz, der die Krebsliga fachlich berät. «Das stellt ein solidarisches Gesundheitssystem vor massive Probleme.» Auch das für die Preisfestsetzung zuständige Bundesamt für Gesundheit spricht gerade mit Blick auf Kombinationstherapien von einer «grossen Herausforderung».

Doch wie die Lösung für das Problem aussehen kann, darüber gehen die Meinungen auseinander. Public Eye schlägt ein radikales Vorgehen vor. Der Bund soll von seiner Möglichkeit Gebrauch machen, eine Zwangslizenz zu erwirken. Dabei wird ein Pharmaunternehmen gezwungen, gegen Entschädigung einen seiner Wirkstoffe von einem Dritten produzieren zu lassen – mit dem Ziel, den Preis zu senken und die Versorgung der Bevölkerung so sicherzustellen.

Roche im Visier

Konkret schlägt Public Eye eine Zwangslizenz für Roches Brustkrebsmedikament Perjeta vor. Unbestritten ist, dass das Mittel einen Fortschritt bringt: In Verbindung mit dem Roche-Medikament Herceptin und einer Chemotherapie verlängert Perjeta das Leben von Brustkrebs-Patientinnen um fünf Jahre – das ist über ein Jahr mehr als beim alten Therapiestandard.

Diese Kombinationstherapie mit drei Wirkstoffen kostet derzeit laut dem Kassenverband Curafutura 8659 Franken pro Monat. Das ist rund doppelt so viel wie der herkömmliche Behandlungsstandard aus Herceptin in Verbindung mit einer Chemotherapie.

Der Preisfestsetzung von Perjeta in der Schweiz ging ein wahrer Krimi voraus. Als Hersteller Roche mit der Preisvorstellung des Bundesamts für Gesundheit 2014 nicht einverstanden war, zog Roche das Mittel zwischenzeitlich vom Markt zurück. Der Preis-Poker zog sich rund ein Jahr hin.

Für Public Eye ist der hohe Preis und Roches Powerplay der Beleg dafür, dass der Konzern aufgrund seiner «monopolartigen Situation» bei Krebsmitteln sich in den Preisverhandlungen durchsetzen kann. Das Bundesamt für Gesundheit und Roche widersprechen. Gerade bei den Kombinationstherapien habe das Amt zuletzt

Preissenkungen bewirken können, teilt es mit. So sanken die Monatspreise für eine Kombinationstherapie Anfang Mai um rund 3,6 Prozent. Dies zeige, dass «auch in der Schweiz für hochpreisige Kombinationstherapien in der Onkologie wirtschaftliche Lösungen gefunden werden können», schreibt ein Sprecher des Amtes.

«Es ist klar, dass bei Kombinationstherapien nicht einfach die Listenpreise der Einzelmedikamente vergütet werden können», sagt Remo Christen, der bei der Schweizer Landesgesellschaft von Roche für die Preisverhandlungen zuständig ist. Dem Bundesamt bescheinigt er eine «konstruktive Haltung», wenn es darum gehe, neue Preismodelle zu finden.

Andreas Schiesser, Pharmaspezialist beim Krankenkassenverband Curafutura, meint dagegen: «Die Behandlung ist – vor dem Hintergrund der in der Schweiz geltenden Regeln – immer noch zu teuer.» Denn der neue Behandlungsstandard sei eben doppelt so teuer wie der früher übliche.

Letztlich wollen Public Eye und die Krebsliga mit ihrem Vorstoss zu einer Zwangslizenz eine Debatte darüber starten, wie die Medikamentenpreise festgelegt werden. Auch der Kassenverband Curafutura sieht hier Reformbedarf, auch wenn er eine Zwangslizenz als zu starken Eingriff ablehnt.

Derzeit läuft die Preisfestsetzung wie folgt ab: Zu Beginn schlägt ein Pharmaunternehmen dem Bundesamt für Gesundheit einen Preis für ein neu zugelassenes Mittel vor. Das Amt zieht zur Preisfestsetzung dann Auslandspreise zum Vergleich heran. Ferner schaut es, was das neue Mittel im Vergleich zu bisherigen Therapien kosten soll. Beide Faktoren werden je hälftig gewichtet. Bei Therapiedurchbrüchen kann das Amt einen Innovationszuschlag zubilligen. Das Amt holt zudem eine Empfehlung der Eidgenössischen Arzneimittelkommission ein, ob ein neues Mittel von den Kassen erstattet werden soll. In der Kommission sind auch Patientenvereinigungen und Krankenkassen vertreten.

«Die Preisfestsetzung läuft in der Schweiz zu intransparent», kritisiert Onkologe Thomas Cerny. Die Krankenkassen wiederum stört, dass sie bei diesen Verhandlungen kaum etwas zu sagen haben. Ist ein Pharmaanbieter mit dem vom Amt festgesetzten Preis nicht zufrieden, kann er Beschwerde einlegen. Die Versicherer dürfen das nicht. Um das zu ändern, ist derzeit eine Initiative im Nationalrat hängig. Die Pharmaindustrie will davon aber nichts wissen. Wie genau sie ihre Preise berechnet, bleibt eines ihrer am besten gehüteten Geheimnisse.

Tages-Anzeiger, 23.05.2018

Philomena Colatrella: Krankenkassen-Chefin mit Mut zu unbeliebten Ideen

Unter der Führung von Philomena Colatrella ist die Krankenversicherung CSS zum grössten Grundversicherer aufgestiegen. Die Juristin fordert mehr Effizienz von der eigenen Branche und mehr Selbstverantwortung von den Versicherten.

Ende der Mittagspause am Hauptsitz der CSS-Krankenversicherung in Luzern: Im Gewusel der Eingangshalle ist Philomena Colatrella leicht zu übersehen. Die Chefin der zweitgrössten Schweizer Krankenversicherung ist eine zierliche Frau.

Obwohl Regen prognostiziert ist, kommt sie im eleganten Tenue: ein Gehrock, blaue Hosen und leichte Sommerschühchen. Das Wetter gibt der Optimistin recht. Wir starten zu einem Bummel an den See. Entlang dem Alpenquai wollen wir in Richtung Richard-Wagner-Museum laufen.

Hitzige Debatte ausgelöst

Ich frage Colatrella, ob wir gleich jenes Thema anpacken wollen, das ihr in den letzten Wochen viele negative Schlagzeilen beschert hat. In einem Zeitungsinterview hatte sie laut darüber nachgedacht, welchen Effekt ein allgemeiner Selbstbehalt von 5000 bis 10 000 Fr. auf die Krankenversicherungsprämien und die wachsende Nachfrage nach Gesundheitsleistungen haben würde. Kurz darauf offenbarte ein Branchenvergleich, welche stattlichen Löhne die Krankenkassen-Chefs erhalten.

Das Echo auf Colatrellas Hypothese war denn auch gewaltig - und vorwiegend ablehnend. «Ich habe die Brisanz des Themas in der Öffentlichkeit unterschätzt. Meine Aussage war als Diskussionsbeitrag und Denkanstoss gedacht. Ich bin zutiefst überzeugt, dass unsere Krankenversicherung auf zwei Säulen basiert: der Solidarität und der Selbstverantwortung. Die Solidarität in unserem System ist zentral. Aber ich fürchte, dass sie mit dem ungebremsten Leistungsausbau ausgehöhlt werden könnte. Deshalb müssen wir die Eigenverantwortung stärken sowie verbindliche Kostenziele in Betracht ziehen.»

Und wie sollen Familien, Chronischkranke oder Leute mit tiefen Löhnen das Risiko der höheren Belastung tragen? Eine Halbierung der Prämien wäre ja gut und schön, aber was bringt das, wenn im Krankheitsfall der Ruin droht? «Selbstverständlich müssen höhere Kostenbeteiligungen mit einer Absicherung sozial Schwächerer und Chronischkranker einhergehen.» Als Tochter eines langjährigen Gewerkschaftsvertreters liege ihr unsoziales Denken fern. Wir machen einen Schritt vorwärts, ebenso wie die Schweizer Gesundheitspolitik. Vor wenigen Tagen eröffnete der Nationalrat die Vernehmlassung zur einheitlichen Finanzierung von ambulanten und stationären Leistungen. Gelänge die Neuordnung der Finanzströme, könnte viel Verschwendung im System eliminiert werden.

Als Vizepräsidentin von Curafutura, dem jüngeren der zwei Krankenversicherungsverbände, hat die Colatrella Seite an Seite mit dem späteren Bundesrat Ignazio Cassis gearbeitet. Sie schätzt ihn sehr und erhofft sich von ihm eine starke Stimme im Bundesrat bezüglich Reformen, auch wenn das Gesundheitsdossier bei Bundesrat Alain Berset liegt. Auch der hat bei ihr gerade gepunktet. «Die Reform der Ärztetarife Tarmed gegen den Widerstand der Mediziner war mutig.» Die Krankenversicherung sehe den Effekt bereits bei den Abrechnungen.

Wachstumskurs für CSS

Die 49-jährige Schweizerin mit italienischen Wurzeln arbeitet seit fast zwanzig Jahren bei der CSS. Als junge Juristin fing sie im Rechtsdienst an. An die Konzernspitze stiess sie vor nicht ganz zwei Jahren. Davor prägte sie schon als Generalsekretärin den Versicherungskonzern. Sie erdachte die Struktur der Holding, unter deren Dach heute eine Reihe von Krankenversicherungen mit unterschiedlichen Formaten Platz findet. «Ich finde diese Arbeit des strategischen Denkens und Umsetzens etwas vom Spannendsten», sagt sie.

Dass sie sich für die Aufgabe als Konzernchefin beworben habe, sei nur konsequent. «Als Frau kann ich nicht immer darüber klagen, dass es so wenige weibliche Führungskräfte gibt, und dann selber nicht vortreten, wenn sich die Chance ergibt.»

Sie freut sich über den Vertrauensbeweis des CSS-Verwaltungsrats. Ihre Anerkennung in der männerdominierten Branche und vielleicht auch im eigenen Unternehmen muss sie sich trotzdem vermutlich noch erkämpfen. Ihr Vorgänger führte die CSS über 15 Jahre in bedächtiger Art und ohne allzu viel Staub aufzuwirbeln.

Colatrella riskiert im Gespräch dagegen schon einmal eine Aussage, die gegen übliche Branchendogmen verstösst. Etwa, wenn sie zugibt, dass der Fokus der Krankenversicherer auf die Medikamentenpreise teilweise überholt sei. «Die Arzneikosten sind weniger stark gestiegen als andere, grössere Kostenblöcke.»

Wir bleiben wieder stehen, und Colatrella schildert, wie sie versucht, als Chefin ihr südländisches Temperament zu zügeln. Es ist klar: Der

Typ des stoischen Versicherungsmannes, der keine Meinung hat und, wenn er eine hat, sie nicht äussert, gehört nicht zu ihren liebsten Mitarbeitern. Seit Übernahme der Geschäftsleitung hat sie denn auch in der Chefetage eine ganze Reihe von Wechseln vorgenommen.

Colatrella rühmt ihre CSS, die stetig an der Effizienz der Verwaltung arbeite und «nur noch 4% der Prämiensumme» für die Verwaltung der Grundversicherung benötige. Der Branchendurchschnitt liegt bei über 5%. Ich halte ihr vor, dass es einfach sei, den stets gleichen Prozentsatz an Verwaltungskosten auszuweisen, wenn die Prämiensumme jedes Jahr steigt. In absoluten Zahlen wüchsen damit die Verwaltungskosten auch an. Colatrella nickt. «Deshalb haben wir unseren Anteil im Vergleich zur Konkurrenz deutlich gesenkt, und daran werden wir weiterarbeiten.»

Sie fordert nicht nur intern Effizienzverbesserungen ein. Die CSS-Krankenversicherung hat auch die Kontrolle bei den jährlich 16 Mio. eingereichten Rechnungen deutlich verschärft. Überhöhte und falsch deklarierte Abrechnungen seitens Spitälern und Ärzten unter den täglich eingereichten 40 000 Belegen seien keine Seltenheit. Letztes Jahr konnte die CSS dank Kontrollen rund 700 Mio. Fr. an fakturierten Leistungen einsparen. «Die Massnahme kommt den Versicherten zugute. So können wir das Wachstum der Prämien bremsen.»

Die im Vergleich zur Konkurrenz langsamer ansteigenden Prämien haben der CSS in den letzten Jahren Zulauf beschert. Mit rund 1,7 Mio. Grundversicherten haben die Luzerner den langjährigen Branchenführer Helsana überholt. Mit 6,17 Mrd. Fr. Prämieneinnahmen bewegt sich die CSS-Gruppe (fast) auf Augenhöhe mit dem Konkurrenten.

Das Ende der Fahnenstange ist für Colatrella noch nicht erreicht. Die Versicherungschefin zeigt sich überrascht, dass die Branche angesichts steigender finanztechnischer Auflagen nicht schneller konsolidiert. «Ich glaube nicht, dass wir in zehn Jahren immer noch gut 60 Krankenversicherungen in der Schweiz haben.» Die Art, wie sie dies sagt, lässt durchblicken, dass sie mit der CSS gern eine aktive Rolle spielen würde.

NZZ am Sonntag, 02.06.2018

Ärzte fürchten den Druck sterbewilliger Patienten

Die Zürcher Ärztegesellschaft fordert ein Bundesgesetz zur Sterbehilfe.

Die Schweizerische Akademie der Medizinischen Wissenschaften (SAMW) hat die medizinethischen Richtlinien zur Suizidbeihilfe gelockert. Neu soll ein Arzt Sterbehilfe leisten können, wenn ein Patient sein Leiden wegen einer Krankheit oder Einschränkung als unerträglich empfindet. Gemäss bisheriger ärztlicher Standesregel darf ein Arzt das tödliche Mittel Pentobarbital nur verschreiben, wenn der Patient an einer unheilbaren tödlichen Krankheit leidet.

Die SAMW hat die Lockerung der Sterbehilferichtlinien jedoch gegen den Willen der Ärzteschaft vorgenommen. Für die Ärzteverbindung FMH führt das Kriterium, dass ein Patient «unerträglich leidet», in eine rechtliche Grauzone. Die Zürcher Ärztegesellschaft fordert aufgrund der Lockerung eine gesetzliche Regelung der Sterbehilfe auf Bundesebene. «Die SAMW macht die Beihilfe zum Suizid zu einer ärztlichen Tätigkeit, unabhängig davon, ob jemand an einer tödlichen Krankheit leidet», kritisiert Josef Widler, Präsident der Ärztegesellschaft des Kantons Zürich.

Widler befürchtet, dass der Druck auf die Ärzte steigen wird. Die Ärzte könnten einem Patienten die Suizidbeihilfe nicht mehr mit Verweis auf die Standesregeln verweigern, wenn sie die Sterbehilfe für fragwürdig hielten. Entscheidend sei künftig der vage Begriff des «unerträglichen Leidens». Massgebend sein würden die Einschätzung des Patienten und dessen Wertvorstellungen. «Das macht es für den Arzt sehr schwer, eine klare Grenze zu ziehen.»

Abgabestelle für Pentobarbital?

Widler fordert deshalb eine gesetzliche Regelung. Dort müssten die Bedingungen festgelegt werden, gemäss denen Sterbehilfe zulässig sei. Die Beurteilung müsse einer zuständigen Stelle übertragen werden, statt die Ärzte damit zu beauftragen. Das Pentobarbital müsste nach Widlers Vorstellungen dann an einer Abgabestelle abgeholt werden.

Die Richtlinien der SAMW werden in der Regel in die Standesordnung der FMH aufgenommen und damit für deren Mitglieder verbindlich. Allerdings verschreiben einige Ärzte in der Schweiz auch heute schon Pentobarbital an Patienten, die nicht todkrank sind. Sie riskieren damit standesrechtliche Sanktionen. Gegen das Gesetz verstösst ein Arzt mit der Beihilfe zum Suizid allerdings nicht, solange er nicht aus «selbstsüchtigen Beweggründen» handelt – etwa um sich zu bereichern.

Eine gesetzliche Regelung der Sterbehilfe und der Sterbehilfeorganisationen wie Exit oder Dignitas wurde im Parlament bereits verschiedentlich diskutiert, bis jetzt aber immer verworfen. 2012 sprachen sich National- und Ständerat gegen Verschärfungen aus. CVP-Nationalrätin Ida Glanzmann gehörte 2012 zu jenen, die sich für strengere Regeln einsetzten. Glanzmann geht denn auch die neue SAMW-Richtlinie zu weit. Sie überlege sich, im Parlament erneut eine gesetzliche Regulierung der Sterbehilfe zu fordern. Zunächst wird sie aber vom Bundesrat eine Stellungnahme zu den neuen Richtlinien verlangen. Mit der Lockerung der Richtlinien fehle den Ärzten eine Grundlage, wenn sie einem Patienten die Suizidbeihilfe verweigern wollten, kritisiert Glanzmann.

«Es gibt ein Recht auf Sterben»

Für die SP-Nationalrätin Bea Heim sollten die SAMW-Richtlinien Anlass sein, die Bedingungen für ein würdevolles Leben im Alter zu verbessern. Es müsse mehr in die Palliativmedizin investiert und mit besserer Betreuung die Vereinsamung alter Menschen verhindert werden. «Dann kommt es auch weniger zu Verzweiflungssuiziden im Alter.»

FDP-Ständerat Andrea Caroni sieht keinen Bedarf für eine gesetzliche Regelung. «Zum Recht auf Leben gehört auch das Recht auf Sterben. Was unerträgliches Leiden ist, kann nur der Patient selber entscheiden.» Der Arzt könne auch mit der neuen SAMW-Richtlinie selbstbestimmt entscheiden, ob er Suizidbeihilfe leisten wolle oder nicht.

Tages-Anzeiger, 08.06.2018

Kommentar der Redaktion

Laut Sonntagszeitung (20.05.2018, Seite 35-36) ist Frau Colatrella diejenige Person, die von allen Krankenkassenchefs am meisten verdient. Gemäss dieser Veröffentlichung beträgt ihr jährlicher Lohn 743‘766 Franken pro Jahr, also deutlich mehr als die Löhne der Bundesräte. Bei so einem Jahresgehalt verwundert es dann auch nicht, dass sie solch unglaubliche, unsoziale Massnahmen, wie die Erhöhung der jährlichen Franchise auf 5‘000 bis 10‘000 Franken, vorschlägt. Also nicht nur ihr Verdienst, sondern die ganze Struktur unseres Gesundheitssystems würde dann fast gänzlich veramerikanisiert. Auf diese Weise würden wir uns von einem relativ zivilisierten zu einem viel weniger zivilisierten Land hinbewegen... Ist das gewollt?

Franco Cavalli

Kommentar der Redaktion

Dieser im Tages-Anzeiger erschienene Artikel enthält verschiedene Punkte, die nicht diskussionslos angenommen werden können. Zu behaupten, «die SAMW habe die Lockerung der Sterbehilferichtlinien gegen den Willen der Ärzteschaft vorgenommen», wie dies der Journalist schreibt, ist völlig falsch. Erstens hat die SAMW eine sehr breite Vernehmlassung zum ersten Vorschlag veranstaltet und aufgrund der Resultate verschiedene Verbesserungen angebracht. Zweitens haben in den letzten Jahren verschiedene Umfragen gezeigt, dass die Mehrheit der Ärzte mit einer solchen Stellungnahme einverstanden ist. Auch im Rahmen der SAMW-Vernehmlassung hat sich die Mehrheit ganz eindeutig dafür ausgesprochen; in der Schlusssitzung des Senats der SAMW gab es praktisch keine Opposition.
Zurzeit ist die FMH, wie auch die Ärztegesellschaft des Kantons Zürich, äusserst konservativ eingestellt. Das berechtigt aber immer noch nicht zu behaupten, wie dies die FMH tut, das Kriterium des «unerträglich leidenden» Patienten führe in eine rechtliche Grauzone, auch weil das Gesetz überhaupt nicht verlangt, dass der Patient leiden muss, um Beihilfe zum Suizid leisten zu dürfen.
Die Leitung der FMH und die Ärztegesellschaft des Kantons Zürich stört scheinbar vor allem, dass künftig «die Einschätzung des Patienten und dessen Wertvorstellungen massgebend sein würden», was hingegen absolut normal sein sollte. Zum Glück sind die Zeiten vorbei, in welchen die Wertvorstellungen des Arztes im Vordergrund standen und diese dem Patienten aufoktruiert wurden.
Völlig unverständlich scheint mir ausserdem der Wunsch von Dr. Widler, Präsident der Ärztegesellschaft des Kantons Zürich, wonach eine neue gesetzliche Regelung notwendig sei und die Beurteilung «einer zuständigen Stelle» übertragen werden müsste, anstatt die Ärzte damit zu beauftragen. Wer diese Stelle leiten und wie sie funktionieren sollte, hiervon ist aber keine Rede. Es wäre auch sehr schwierig, so eine Stelle zu organisieren, ohne in eine völlig unverantwortliche Bürokratie zu verfallen.
Die neuen Richtlinien wurden in den Medien und, soweit man es beurteilen kann, auch in der Öffentlichkeit äusserst positiv bewertet. Die FMH und die Herren der Ärztegesellschaft des Kantons Zürich sollten nicht vergessen, dass die Bevölkerung (vor allem in Zürich!) jedes Mal, bei jeder Abstimmung immer und eindeutig die Beihilfe zum Suizid befürwortet hatte, so wie sie im Gesetzbuch verankert ist. Und das Gesetzbuch ist immer noch liberaler als die neuen Richtlinien der SAMW!

Franco Cavalli

«Les autorités doivent protéger les malades, pas les brevets»

Partout en Europe, au Japon ou aux États-Unis, la pression monte sur l'industrie pharmaceutique. Qu'elle provienne des gouvernements, par exemple de l'administration Trump, de la France, du Royaume-Uni ou de la ministre hollandaise de la Santé – la pourtant très libérale Edith Schippers, qui mène une campagne identique à celle lancée mardi par l'ONG helvétique Public Eye (ex-Déclaration de Berne), intitulée «Pour des médicaments à prix abordables» –, le désamour face aux pharmas grandit.

Car, comme l'affirme Franco Cavalli, oncologue et ancien président de l'Union internationale contre le cancer, «la question de l'accès à un traitement se pose désormais également dans les pays riches».

Soins à 300'000 francs

Le médecin tessinois sait de quoi il parle: la prescription d'un nouveau médicament anticancéreux coûte aujourd'hui quelque 100'000 francs par an à l'assurance de base helvétique, «voire 300'000 francs annuels s'il est combiné avec d'autres produits». Or, et même si les cas sont encore rares, selon le président de la Ligue suisse contre le cancer, Gilbert Zulian, «l'accès aux nouveaux traitements, pourtant validés par l'Office fédéral de la santé publique, devient de plus en plus difficile, en raison des coûts».

Les sociétés civiles et certains États développés se mobilisent soudain, dans les traces plus anciennes de l'Inde, du Brésil ou de nombre de pays africains. En Suisse, ce sont donc aujourd'hui Public Eye et la Ligue suisse contre le cancer qui attaquent le problème. Ces deux associations ont donné, mardi, le top départ à une campagne nationale qui interpelle en premier lieu le Conseil fédéral. «Les autorités suisses doivent protéger les malades, pas les brevets», affirme ainsi Patrick Durisch, responsable du secteur santé chez Public Eye. Qu'est-ce à dire? Cet appel collectif demande au gouvernement helvétique «d'utiliser la licence obligatoire pour lutter contre les prix exorbitants des médicaments». Il s'avère, en effet, que ce concept de licence obligatoire – un instrument prévu par le droit international des brevets – permet aux États membres de l'Organisation mondiale du commerce (OMC) d'autoriser un tiers, par exemple un fabricant de génériques, à produire et commercialiser un produit similaire, et ce malgré l'existence d'un brevet.

«Pour cela, affirme Ellen't Hoen, spécialiste hollandaise en droit de la propriété intellectuelle, pas besoin d'une situation de pandémie, comme ce fut le cas avec le virus du sida, de la grippe aviaire ou Ebola aujourd'hui.» Le recours à la licence obligatoire est juridiquement possible dès lors que l'équilibre entre les intérêts d'une industrie très rentable et les besoins de santé publique est rompu. Or, l'ancienne conseillère fédérale en charge de la Santé et soutien actif de cette campagne Ruth Dreifuss estime sans ambages que cet équilibre est rompu.

Trop de zones d'ombre

La Genevoise a ainsi été appelée par l'ex-secrétaire général des Nations Unies, Ban Ki-moon, pour réfléchir, avec d'autres experts, dont le Prix Nobel d'économie Joseph Stiglitz, à cette question d'accès mondial aux soins, sans briser l'innovation. «Dans le rapport que nous avons livré en septembre 2016, déclare-t-elle, nous avons clairement affirmé notre soutien au principe des brevets et, donc, au respect de la propriété intellectuelle.» Mais, selon elle, il existe encore tant de zones d'ombre dans l'industrie pharmaceutique – en premier lieu la transparence des coûts de recherche pour un médicament et sa réelle plus-value thérapeutique – qu'on peine à lui donner un blanc-seing. «Lorsque j'étais en charge de la Santé publique en Suisse, dénonce encore Ruth Dreifuss, je n'avais accès à aucune donnée précise, expliquant pourquoi tel ou tel nouveau traitement allait coûter des dizaines, voire des centaines de milliers de francs par année. Je devais signer d'une main, tandis que l'autre était attachée dans mon dos.»

À l'instar des pays pauvres – où l'accès universel aux soins n'est qu'une vaste plaisanterie –, les pays riches se voient eux aussi forcés d'imposer à leurs pharmas de livrer leurs secrets de fabrication, dont ils resteraient, certes, propriétaires, mais que les États pourraient saisir, en leur versant une contrepartie financière. Lundi, en marge de l'ouverture de l'Assemblée mondiale de la santé, à Genève, le ministre de l'Intérieur, Alain Berset, a reconnu que «des efforts législatifs devaient être menés» pour améliorer l'accès aux génériques. Et puis, silence.

24 Heures, 23 mai 2018

Espérance de vie: une tragédie américaine

Qui l'eût cru? Pour la première fois de l'histoire moderne, il est plus sûr de naître en Chine qu'aux Etats-Unis, si l'on veut vivre longtemps en pleine forme. Selon les dernières données de l'Organisation mondiale de la santé, dévoilées par l'agence Reuters, un bébé chinois peut espérer vivre 68,7 ans en bonne santé, contre 68,5 ans pour un Américain.

Pour le moment, en matière d'espérance de vie totale, les Etats-Unis restent devant, à 78,5 ans, contre 76,4 ans en Chine, mais l'information confirme une tendance observée depuis quelques années: la santé se dégrade aux Etats-Unis. En décembre 2017, les Centres américains de contrôle et de prévention des maladies (CDC) avaient pointé cette triste réalité dans leur rapport annuel. Pour la première fois depuis 1963, l'espérance de vie a diminué deux années de suite dans le pays, en 2015 et 2016.

Il ne s'agit pas d'un mouvement général, mais spécifiquement américain, même si tous les pays occidentaux connaissent un tassement de l'espérance de vie en bonne santé. Seuls cinq pays ont connu une chute en 2016: le pays le plus riche de la planète rejoint la Somalie, l'Afghanistan, la Géorgie et l'archipel de Saint-Vincent-et-les-Grenadines. A l'inverse, les bébés singapouriens, japonais ou suisses sont les plus chanceux du classement et les pays d'Asie sont ceux qui connaissent la plus forte amélioration, reflet de leur santé économique. L'espérance de vie aux Etats-Unis est aujourd'hui en dessous de celle de l'OCDE et plus proche de celle de la Turquie que des pays européens.

L'origine de cette situation est identifiée. Selon le CDC, c'est l'explosion des décès par overdose de drogue (essentiellement les opioïdes) aux Etats-Unis. Avec 63 000 morts en 2016, ils sont devenus la troisième cause de mortalité dans le pays derrière les maladies cardiaques et les cancers. Loin derrière, mais comme ils sont concentrés sur des populations jeunes, ils ont un effet puissant sur les statistiques. La mortalité par drogue chez les 25-34 ans a explosé de 50% entre 2014 et 2015. Et comme la tendance s'est poursuivie en 2017, ce serait le plus profond déclin de l'espérance de vie aux Etats-Unis depuis l'épidémie de grippe espagnole qui a ravagé le monde au tournant des années 1920.

Explosion des inégalités

La forme de délitement social que traduit cette épidémie n'est pas pour rien dans l'essor du populisme américain qui a porté Donald Trump au pouvoir. Ce dernier avait d'ailleurs promis un grand plan de lutte contre les drogues, qui n'a pas encore vu le jour. L'explosion des inégalités, la faiblesse des couvertures sociales et la qualité médiocre de l'enseignement initial ont joué probablement un rôle-clé dans cette nouvelle tragédie américaine.

Pour l'instant, le gouvernement américain semble s'intéresser plus à défaire les régulations mises en place après la crise financière de 2008 pour contenir les ambitions spéculatives des banques qu'à s'attaquer à un problème de société qui menace à terme la prospérité de la première puissance économique mondiale.

Le Monde, 1 juin 2018

Cancérologie: la percée des cellules CAR-T se confirme

ASCO a réaffirmé les promesses de cette immunothérapie innovante dans des cancers du sang. Trois défis demeurent: sa sécurité, son modèle économique et son déploiement contre des tumeurs solides.

…«*La thérapie par cellules CAR-T est sur le point de transformer le pronostic d'enfants et d'adultes atteints de cancers jusqu'ici incurables*», déclarait, en janvier, la Société américaine d'oncologie clinique. Et l'ASCO de consacrer cette stratégie «avancée thérapeutique de l'année», en 2017.

Elle repose sur ce principe: des globules blancs, les lymphocytes T du patient, soldats de l'immunité, sont prélevés, cultivés in vitro, puis modifiés génétiquement de manière à leur faire exprimer un récepteur artificiel (le «CAR»), qui reconnaît spécifiquement les cellules de la tumeur à combattre. Après un délai de plusieurs semaines, ils sont ensuite réinjectés au patient, prêts à tuer ce cellules.

Tout commence en Israël, à l'Institut Weizmann des sciences. «*Quand nous avons conçu le modèle des premières cellules CAR-T, dans les années 1980 et au début des années 1990, un dogme voulait que les lymphocytes T n'aient qu'une efficacité limitée contre le cancer*», se souvient le professeur Zelig Eshhar, du Weizmann, dans la revue *Human Gene Therapy*. Son équipe montrera pourtant l'efficacité anticancer de cette approche chez la souris.

De la souris à l'homme, le chemin est semé d'embûches. En 2005, un premier essai chez l'homme se solde par un échec contre des cancers du rein. Retour à la paillasse: le modèle des cellules CAR-T est peaufiné, on lui ajoute une autre pièce de Lego.

En 2011, la stratégie montre enfin son efficacité chez l'homme, contre des leucémies ou les lymphomes «à cellules B» agressifs. Cette percée sera réalisée par les équipes américaines de Carl June, de l'université de Pennsylvanie, de Michel Sadelain, du Memorial Sloan-Kettering Cancer Center, à New York, et de Steven Rosenberg, du National Cancer Institute, à Bethesda.

En 2017, la toute-puissante agence du médicament américaine, la Food and Drug Administration, autorise les deux premières thérapies par cellules CAR-T: le Kymriah (Novartis) contre une leucémie rare réfractaire aux traitements classiques chez les moins de 25 ans – son indication sera élargie en mai 2018 au «lymphome diffus à grandes cellules B». Et le Yescarta (Kite Pharma, racheté par Gilead), contre un lymphome agressif chez l'adulte. «*L'autorisation européenne de ces deux traitements est attendue cette année*», espère Nicolas Boissel.

La dernière édition de l'ASCO confirme l'intérêt chez l'homme d'une autre thérapie par cellules CAR-T (développée par Bluebird Bio, et dont Celgene a acquis la licence) dans un autre cancer du sang, le myélome multiple.

Indications encore limitées

Cet enthousiasme doit être tempéré. «*Il y a un énorme lobbying et beaucoup de buzz autour de cette stratégie*, convient Aurélien Marabelle. *Pour l'heure, ses indications restent limitées à certains cancer du sang.*» Ces traitements sont très lourds: le patient doit commencer par subir un conditionnement par chimiothérapie, «*presque comme pour une greffe de moelle*», même si les cellules CAR-T proviennent de son organisme. «*L'organisation de ces parcours de soins n'est pas simple*», témoigne Nicolas Boissel…

Mais le principal talon d'Achille de ce remède vient de sa toxicité, qui peut être fatale. Il peut entraîner la libération de «flots» de cytokines, molécules du système immunitaire. Cette «tempête de cytokines» peut induire un syndrome pseudo-grippal, «*avec une forte fièvre, une hypotension, voire des défaillances d'organes, qui peut nécessiter une hospitalisation en réanimation*», précise Nicolas Boissel…

Autre frein majeur: le modèle économique de ce traitement n'est «*pas tenable*», juge le professeur Eric Vivier, immunologiste à Aix-Marseille (AP-HM) et directeur scientifique d'Innate Pharma. Le coût du traitement, à partir des cellules du patient, s'élève à plus d'un million de dollars. D'où une stratégie alternative lancée par la start-up française Cellectis, pionnière dans ce domaine: les cellules CAR-T «sur étagère». Au lieu de recourir aux lymphocytes du patient, la méthode fait appel aux lymphocytes de donneurs sains, dits «allogéniques», manipulés à l'avance pour qu'ils ciblent tel ou tel antigène tumoral…

Reste ce troisième défi: démontrer l'efficacité des cellules CAR-T contre des tumeurs solides. «*Les cancers du sang sont plus accessible au système immunitaire que les tumeurs d'organes*», explique Nicolas Boissel. Mais le potentiel de ces cellules commence à être exploré dans des tumeurs du cerveau, ou «gliomes», qui touchent surtout les enfants. Selon un article publié le 16 avril, également dans *Nature Medicine*, des cellules CAR-T ciblant un antigène (GD-2) sont efficaces pour éliminer ce type de tumeurs chez la souris. Reste à faire la preuve d'une telle efficacité chez l'homme…

Le Monde, 6 juin 2018

Un nouveau Graal pour l'industrie?

Les Big Pharma déploient les grandes manœuvres. En septembre 2017, Gilead a investi 11,9 milliards de dollars (environ 10 milliards d'euros) pour racheter Kite Pharma, un des pionniers de la thérapie par cellules CAR-T. En décembre, Janssen (Johnson&Johnson) a annoncé sa collaboration avec la biotech chinoise Legend. En janvier, Celgene rachetait pour 9 milliards de dollars Juno Therapeutics, expert de la technologie CAR-T. Le géant Pfizer, de son côté, a recruté des anciens de Kite Pharma pour monter Allogene Therapeutics. Et, en mai, Gilead annonçait la création d'une plate-forme de production du Yescarta aux Pays-Bas. Parallèlement à ces traitements à partir des propres cellules du patient, les CAR-T venant de donneurs sains ont aussi la cote. Cinq essais cliniques sont en cours avec cette approche chez Cellectis. Selon André Choulika, son cofondateur et PDG: «*Novartis, Gilead, Celgene… sont en train de se mettre aux CAR-T allogéniques. C'est la prochaine vague, très compétitive, qui se joue.*»

Le Monde, 6 juin 2018

Emploi, vie de couple… quelle vie cinq ans après un cancer?

4 179 personnes ont répondu à l'enquête de l'Institut national du cancer

Vie professionnelle, état de santé, sexualité… Comment vit-on cinq ans après un diagnostic de cancer? L'Institut national du cancer (INCa) et l'Institut national de la recherche et de la santé médicale (Inserm) ont dévoilé, mercredi 20 juin, les résultats de «VICAN5», une enquête extrêmement détaillée menée en 2015 auprès de 4 179 personnes âgées de 23 à 87 ans auxquelles un cancer avait été diagnostiqué cinq ans plus tôt.

Objectif de l'étude, dont une première édition – réalisée en 2012 et publiée en 2014 – portait sur la vie deux ans après la découverte de la maladie: mieux connaître les conditions de vie des quelque trois millions de Français qui vivent avec un cancer ou en ont guéri. «*L'épreuve du cancer ne se limite pas au seul traitement de la maladie»,* soulignent les auteurs de l'enquête. Pour eux, le diagnostic «*marque souvent une rupture biographique importante qui inaugure une ère nouvelle pour les personnes atteintes*»…

Les séquelles

Cinq ans après le diagnostic, près des deux tiers des répondants (63,5%) assurent avoir conservé des séquelles de leur maladie. Parmi les principaux troubles évoqués: des modifications de l'image du corps, des douleurs, une fatigue chronique, des troubles moteurs ou de la vision. «*Ces personnes sont sorties de la phase de traitement, mais ont encore besoin de soins»,* relève Patrick Peretti-Watel, directeur de recherche à l'Inserm et coresponsable scientifique de l'étude.

La séquelle la plus citée est la fatigue, jugée par près de la moitié des répondants (48,7%) comme le symptôme clinique le plus significatif. Cette fatigue est davantage présente chez les femmes que chez les hommes, et est davantage rencontrée chez les personnes en situation de précarité. Près de trois quarts des personnes interrogées (73%) disent par ailleurs avoir ressenti des sensations douloureuses au cours des quinze jours précédant l'enquête.

Ces différents troubles, plus ou moins graves, perturbent la vie quotidienne, affectent la qualité de vie et peuvent devenir «*dévastateurs par leurs répétitions ou par un jeu de cumul*», relève l'étude. Or à peine un quart des malades (26,1%) estiment bénéficier d'un suivi médical ou paramédical pour ces symptômes.

La qualité de vie

Tous les cancers n'ont pas le même impact sur la qualité de vie physique, c'est-à-dire la façon dont le malade perçoit son état de santé. Cinq ans après le diagnostic, deux tiers des personnes qui ont eu un cancer des poumons (66,5%) se plaignent d'une qualité de vie «dégradée», suivis de ceux atteints d'un cancer du col de l'utérus (60,8%), d'un cancer des voies aérodigestives supérieures (55%), et d'un cancer du sein (50,9%).

Une perception qui ne connaît «*aucune évolution significative*» entre deux et cinq ans après le diagnostic. «*Il y a une stabilisation de la dégradation de la qualité de vie, les gens ne vont pas mieux mais ne vont pas moins bien*», résume Patrick Peretti-Watel.

L'emploi

L'étude permet de mesurer très finement l'impact du cancer sur la vie professionnelle des malades. En cinq ans, le taux d'emploi chez les malades baisse de plus de dix points, passant de 87,3% à 75,9%. En tenant compte du fait que les personnes en arrêt maladie restent administrativement en situation d'emploi, c'est une personne sur cinq qui ne travaille pas cinq ans après un diagnostic de cancer. Cette «*détérioration de la situation professionnelle*» est «*plus importante*» que celle constatée lors de la précédente enquête, réalisée deux ans après le diagnostic, note l'étude, qui acte une «*accélération*» du phénomène de sortie d'emploi.

«*Il semblerait ainsi que l'impact du cancer sur la vie professionnelle puisse survenir à moyen terme*», constatent les auteurs de l'étude, mettant notamment en avant les temporalités des différentes phases de protection sociale, l'arrêt-maladie pouvant par exemple durer jusqu'à trois ans. Pour Patrick Peretti-Watel, «*la troisième année après le diagnostic est une année pivot, c'est celle où l'on observe pas mal de pertes d'emplois*».

De façon générale, parmi les plus exposés, on trouve les travailleurs exécutants, les salariés du secteur privé, les individus travaillant dans les très petites entreprises, les actifs les plus jeunes et les plus âgés, les chefs d'entreprise et les personnes ayant connu un diagnostic de cancer du poumon, des voies aérodigestives supérieures ou un cancer colorectal.

La vie affective et conjugale

La vie de couple «*semble relativement préservée*», souligne l'étude, les participants en «*couple stable*» faisant état d'une relation identique (52,8%) ou renforcée (35,5%) plutôt que dégradée (10,7%) par rapport à avant le diagnostic. Les participants aux deux enquêtes (en 2012 et 2015) estiment par ailleurs que les troubles sexuels ont eu plutôt tendance à augmenter. Plus de la moitié (56,8%) font état d'une baisse de leur libido (sauf chez les 18-40 ans), de leur capacité à avoir un orgasme (53,8%) et de la fréquence de leurs rapports sexuels (64,8%), des réponses très variables selon le type de cancer.

Le Monde, 21 juin 2018

Drugmakers take unorthodox route to cancer biosimilars

NHS clinicians keen to control costs are working with groups on copycat treatments

Jatinder Harchowal, chief pharmacist at London's Royal Marsden Hospital, the specialist UK cancer centre, does not look like a revolutionary.

But the measured 48-year-old is leading a transformation in the shape and cost of cancer treatment – with large implications for the global pharma industry.

Working with Sandoz, the generics arm of Swiss drugmaker Novartis, he and his colleagues have, in just six months, helped to shift roughly 80 per cent of eligible patients in England to a «biosimilar» version of Roche's blood cancer medicine Rituximab, achieving an estimated £80m in savings for the UK's taxpayer-funded health system.

Yet rather than continuing to use Sandoz's biosimilar, the Marsden has chosen one manufactured by privately owned NAPP Pharmaceuticals, which brought the first Rituximab copycat to market last year.

Sandoz's decision to invest in a project to educate physicians and patients about copycat versions of biologic drugs – medicines made from living cells – with no guarantee of an immediate commercial return, underlines the potential it sees in a market which it says will be worth $14bn by 2020.

Building confidence among doctors and patients through such initiatives is sees as crucial to the take-up of biosimilars, especially in oncology. Sensitivities often stem from the fact that very minor differences in components from the originator drug are permitted.

Emphasising that the work would not have happened without the resources Sandoz was able to commit, Mr Harchowal said: «We felt that to engage the clinical mind and heart, you had to really, really make sure people understood how biosimilars… were offering the exact same clinical effective outcomes, with the same safety profile but at a potentially much cheaper cost.»

The European Medicines Agency sanctioned its first biosimilar more than a decade ago and has a highly developed regulatory framework, in contrast to the US where far fewer products have so far been approved.

Keen to control costs, health systems across Europe are embracing biosimilars but Mr Harchowal said the UK was far ahead of most of the rest of the continent in the scale of its biosimilar switch.

Some of the bestselling biologics are set to lose exclusivity in the coming year, including AbbVie's rheumatoid arthritis drug Humira which had sales of $4bn in Europe in 2017. The first biosimilar version is likely to be available by the end of this year. But as the work at the Marsden – in partnership with University College London Hospitals and the Christie in Manchester – demonstrates, the big opportunity is in biosimilars used to treat cancer.

The three biggest selling cancer drugs in Europe have had biosimilar versions approved in the past few months: Rituximab; another Roche drug, Trastuzumab, marketed as Herceptin and used to treat breast cancer; and Bevacizumab, marketed as Avastin, which is used to treat a number of cancers and is made by Genentech, a division of Roche.

The Swiss drugmaker's exposure was reflected in a 2 per cent fall in European pharma sales last year.

Explaining Sandoz's participation in the cancer project – with no certainty its own biosimilar would be selected – Tim de Gavre, the company's UK head, said: «We have a vested interest in creating a sustainable environment around biosimilars where we see them being implemented in the right way.»

The shift in the NHS's stance is already evident. In the last financial year, it has saved £170m through the use of three biosimilars – well on the way to a goal set by Simon Stevens, head of the health service in England, to save £300m from this approach by 2021.

However, the concern for companies that invest in biosimilars is that health systems will drive so hard a bargain the venture becomes uneconomic, reducing the very competition that can help to curb spiralling costs. The NHS succeeded in negotiating discounts of up to 60 per cent for Retuximab biosimilars, according to Mr Harchowal.

Chrys Kokino, global biologics head for US drugmaker Mylan, which has seen prices for its generic drugs squeezed, said his company was «very heavily invested [in] and committed to the space in biosimilars». However he added: «If we go down this [route] of triggering price wars between manufacturers, ultimately… some manufacturers may believe that the price has become so low that they will either exit the market or they will selectively only enter certain markets, diminishing the opportunity to trigger competition.» …

Financial Times, 19 April 2018

Minimalism in oncology

Expenses related to cancer treatment can diminish patients' quality of life and impede delivery of highquality care. Thus, it is worrying that, in 2017, a study showed the price of some common cancer drugs in the USA rose at a rate higher than inflation. The US senate has recently started investigating why a 40-year-old cancer drug—lomustine, which has no generic competition—has increased in price by 1400% since 2013. At the 23rd Annual Conference of the National Comprehensive Cancer Network (Orlando, FL, USA, March 22–24, 2018), oncologists had a heated debate about the congressional mandate that prohibits the Centers for Medicaid and Medicare Services from negotiating drug prices with pharmaceutical companies in the USA. Although governmental action is needed to regulate the unit price at which cancer drugs are marketed, could the medical oncology community further help alleviate the financial burden placed on patients by rethinking the way oncology is practiced?

Optimising treatment dose could be central to the financial toxicity debate. For example, a recent trial of abiraterone showed the concentration of drug that enters the bloodstream can be increased by four times if the drug is swallowed with a low-fat meal rather than on an empty stomach. Such a simple change in drug administration can reduce the current standard dose of abiraterone by three-quarters without compromising efficacy. This study supports anecdotal evidence that many oncology drugs could be taken at lower doses or for shorter periods without reducing effectiveness, alleviating both physical and financial toxicity to patients. Another example of successful dose reduction is immunisation against the HPV serotypes 16 and 18, for which two vaccine doses provide similar protection to the initially recommended three-dose schedule.

The life-threatening condition of cancer has traditionally meant that high drug doses, and thereby high toxicity, have generally been considered acceptable if a treatment is effective. The presumed understanding that high dose translates into higher anti-tumour activity still drives clinical trial design, with maximumtolerated doses (MTD; the highest dose of a treatment that does not cause unacceptable side effects) being established as the recommended dose for most new oncology drugs. Although fine-tuning a personalised dose for each patient is neither feasible nor plausible— the optimal dose is just an estimation for a particular patient, and optimisation strategies could substantially delay the market entry of new drugs—rethinking drug development to aim for a minimum-effective dose (MED; lowest dose of treatment that provides a clinically meaningful response) could be a sensible approach to find

the balance between oncological effectiveness, and physical and financial toxicity. Furthermore, in the era of targeted therapies, which differ from cytotoxic chemotherapies in that they follow a non-linear doseresponse saturation curve whereby the addition of more drug does not always improve outcomes, should the way that safety is assessed move away from the traditional pharmacology-driven study designs?

A 2010 pooled analysis of trials of targeted therapy showed that patients treated with low doses (≤25% MTD) had similar outcomes to those treated with intermediate (25–75% MTD) and high doses (≥75% MTD) in terms of survival, objective responses, and toxicity. These findings suggest that receiving the maximum-tolerated dose for many targeted agents could imply overtreatment, and advise departure from the conventional use of maximum dose protocols…

The Value in Cancer Care Consortium—which plans to initiate trials that explore whether the dose, duration, or type of drug can be optimised—is a first, promising step to tackle financial toxicity. However, a more drastic transformation of the way oncology is practiced could start by simply redefining what the effective dose of a new regimen truly is.

The Lancet Oncoloy, May 2018

Trump unveils plan to cut drug prices

The president's wide-ranging plan to reduce prescription drug prices won't be easy to achieve, experts say.

A brass band struck up «Hail to Chief» as President Donald Trump entered the White House Rose Garden 3 weeks ago to unveil what he called «the most sweeping action in history to lower the price of prescription drugs for the American people»…

The president's 44-page plan – *American Patients First: The Trump Administration Blueprint to Drug Prices and Reduce Out-of-Pocket Costs* – includes proposals to improve competition and price transparency and end so-called global freeloading by countries who do not pay their fair share for drugs.

But two changes Trump advocated during the presidential campaign are missing. As the Republican candidate for president, Trump disagreed with his party and supported Americans' ability to buy drugs at cheaper prices from other countries. And he also favoured—while the party opposed—allowing the federal government to directly negotiate lower prices with pharmaceutical companies on behalf of some 60 million older Americans in the federal Medicare programme.

The blueprint is mainly a collection of «small ideas», said Joshua Gordon, policy director at the Concord Coalition, a non-partisan advocacy group for fiscal responsibility. «There is no 'moon shot' here», he said, referring to President John F Kennedy's call to land a man on the moon…

But so far, drug makers have escaped much of the Trump administration's tough talk.

«Companies were worried about the potential impact of the speech and then realised it won't have much of an impact on their bottom line», said Rachel Sachs, an associate professor of law at the Washington University School of Law in St Louis who studies the interaction of intellectual property law, food and drug regulation, and health law. In response to the blueprint, biotech and pharmaceutical stocks went up, she noted.

The Pharmaceutical Research & Manufacturers of America, a trade group representing brand-name drug companies, has said attempts to lower drug prices could backfire, jeopardising drug development and access to affordable drugs, driving up insurance premiums, and restricting coverage…

«Global freeloading»

Americans spend more per capita on generic and brand-name drugs than any other country, according to *Making Medicines Affordable: A National Imperative*, a consensus study report published by the National Academies of Sciences, Engineering, and Medicine earlier this year. In 2010, US expenditures were twice as high as the UK's, which was the lowest of seven nations in a study cited in the report. In addition to paying higher prices for drugs, American taxpayers also foot the bill for drug research.

«It's unfair and it's ridiculous, and it's not going to happen any longer», Trump said to applause in the Rose Garden. «It's time to end the global freeloading once and for all.» Trump said he would direct the US Trade Representative to fix «this injustice» with every trading partner. Although details are still scarce, the USA could leverage trade agreements to pressure foreign countries to pay US drug makers more for drugs. The companies could then use that money to lower US drug prices or perhaps to fund a greater portion of research costs…

So far, it is unlikely that many other countries will cooperate. A European Commission spokesman in Washington, DC, claims the USA is responsible for its problem.
«EU member states have government entities that either negotiate drug prices or decide not to cover drugs whose prices they deem excessive», he said. «Drug manufacturers in the USA set their own prices, and that is not the norm elsewhere in the world.»

A key US ally was even more emphatic. «The UK Government is committed to ensuring patients have access to the medicines they need and that the cost of medicines remains affordable to the National Health Service (NHS)», said a UK spokesperson at the British embassy in Washington, DC. «The NHS is now, and always will be, a public service free at the point of need; it is not, and never will be, for sale to the private sector, whether overseas or domestic; and no trade agreements will ever alter these fundamental facts.»

The Lancet, Vol 391, 2 June 2018

In eigener Sache

Wir haben jetzt die Vorstellung der klinischen Krebszentren in der Schweiz weitgehend beendet. Es fehlt noch ein Zentrum, das wir in N° 4-2018 unseres Bulletins präsentieren werden.

Nun haben wir vor, als neue Serie die wichtigsten Schweizer Krebsforschungszentren im Bulletin vorzustellen: In dieser Ausgabe beginnen wir mit dem AGORA-Zentrum in Lausanne, auch weil dieses am 3. Oktober 2018 feierlich eingeweiht werden wird. Weitere Krebsforschungszentren werden nächstes Jahr folgen.

Die Redaktion

WICHTIGER HINWEIS

Easier drug approval, at what price?

Safety and innovation may be reduced while the cost of new medicines continues to increase.

Dr. Scott Gottlieb, the commissioner of the Food and Drug Administration, recently vowed to bring «new science» to market faster, in hopes that patients benefit from treatment advances sooner.

Medications are already clearing regulatory hurdles faster than ever, but it's not clear that people, as opposed to drug companies, are feeling much benefit. For several years the F.D.A. has been lowering the standards by which it decides whether new medications are safe and useful. The agency now requires fewer and smaller clinical trials, approving some drugs after just one successful trial. It also accepts short-term effects (like whether a drug shrinks a tumor) instead of clear clinical outcomes (like whether the drug prolongs life), and ever-smaller improvements in health as sufficient proof that a medication works and is worth selling.

On its face, this shift seems practical. The nature of pharmaceuticals has changed. Instead of developing broad-spectrum medicines that work for the masses, drugmakers are pursuing personalized therapies that work for — and thus only need to be tested in — much smaller populations whose conditions share the same genetic profiles. That can make large clinical trials seem wasteful.

But, if we're not careful, the changes now underway may do more harm than good.

According to industry watchdogs, reducing clinical trial costs will not help curb list prices because those prices are not determined by investment costs; they're determined by what the makers think the market can bear, which helps explain why profit margins are so high.

Smaller trials also make it more difficult to determine a drug's actual medical value: If you don't know how a medication compares with other treatments, or whether it will actually improve the quality or length of life, how can you possibly know what it's worth?

And lower standards might actually inhibit innovation, by giving companies less incentive to make substantial improvements to their offerings.

Dr. Gottlieb and others say that patients facing long odds and potentially fatal diseases don't have time to wait for more clinical trials. That's a fair point. Reasonable people can disagree over where the fulcrum between speed and evidence should be placed. But a new drug is only innovative if lives are extended or improved, and we can't know if they will be without more data.

Based on the data we do have, the thousand-plus cancer drugs now in clinical development are quite likely to help only a handful of patients, and only a very little bit: According to one recent study, targeted cancer therapies will benefit fewer than 2 percent of the cancer patients they're aimed at. That reality is often lost on consumers, who are being fed a steady diet of winning anecdotes about miracle cures. Those stories are heartening, especially if you or someone you love is one of the people battling the long odds who could be helped. But they omit a lot, including the number of people who aren't saved — or even helped — by a given drug, and the likelihood that any given success would have occurred even without the new medication.

The Food and Drug Administration is still the world's leading regulator of medicine by far, setting the bar for countries around the world. Lest it lose that standing, the agency should demand more of the drugs (not to mention medical devices) it approves.

Requiring at least two successful clinical trials for any drug — as the government did until recently — would be a great start; it would sharply reduce the odds of false positives (drugs that show benefit but only by pure chance). It would also help to set minimum benefit standards, requiring that a drug improve patients' lives and health by a certain, measurable amount.

Another thing federal officials can do is to use independent cost-benefit analysis to set a drug's list price. The United States is the only developed country in the world that doesn't do this, and the result is that the prices patients pay for medications often have little to do with how much benefit is derived from them.

Officials in the past have rejected this approach because of concerns that consumers would be robbed of choice, either because an insurance company would force them to switch from their current medication to one that it determined was fairly priced, or because pharmaceutical companies would choose not to market drugs that they thought were not priced generously enough.

But consumers, who now rank steadily climbing drug prices at the top of their list of health concerns, might be willing to make these trade-offs. At the very least, people who rely on medications deserve a better sense of what they're paying for.

The New York Times Int. Edition, 11 June 2018

Kommentar der Redaktion – Das Problem der Zulassung von Krebsmedikamenten hatten wir bereits in N° 1-2018 des Krebsbulletins von zwei Opinion-Leaders diskutieren lassen (siehe SKB 38: 23-27, 2018). Thomas Cerny behauptete, dass heute Krebsmedikamente zu leicht zugelassen werden, was Roger von Moos hingegen verneinte. Das Thema bleibt sehr aktuell, vor allem weil die Preise der Krebsmedikamente immer weiter steigen. Auch in den USA ist das Thema brisant: Vergessen wir nicht, dass die Medikamentenpreise das Hauptthema in der Auseinandersetzung zwischen Sanders und Clinton bei der Nominierung des demokratischen Kandidaten waren. Und auch Trump hatte während der Wahlkampagne immer wieder davon gesprochen.
Es passiert sehr selten, dass die New York Times in einer Ausgabe nur einen und nicht wie fast immer zwei oder drei Leitartikel veröffentlicht. Daraus kann man folgern, dass das Thema schon sehr wichtig sein muss. Und aus diesem Grund räumen wir diesem Leitartikel auch einen besonderen Platz ein. Was in diesem Artikel irgendwie mitspielt, aber nicht ganz eindeutig herauszulesen ist, ist Folgendes: Das erste Meeting, das Präsident Trump nach seiner Wahl mit Vertretern der «Zivilgesellschaft» hielt, war ein Treffen mit den CEOs der wichtigsten Pharmamonopole. So wie die Gegebenheit dann den Medien kolportiert wurde, sollte sich die Diskussion etwa wie folgt abgespielt haben: Präsident Trump sagte, man müsse schon schauen, dass die Preise der Medikamente nicht weiter steigen oder sogar etwas abnehmen. Darauf antworteten die mächtigen CEOs, dass sie ihr Möglichstes tun würden, vorausgesetzt, die Zulassung neuer Medikamente würde deutlich erleichtert. Und siehe da, die FDA ist dabei, dies zu bewerkstelligen, weswegen die New York Times jetzt so besorgt reagiert. Wer sich in der Branche auskennt, weiss auch, dass seit einiger Zeit, nicht nur in der Onko-Hämatologie, sondern in allen onkologischen Bereichen, Versuche unternommen werden, um z.B. die Definition einer partiellen Remission abzuändern. So spricht man von eindimensionalen Messungen (nicht mehr von dreidimensionalen), von partieller Remission (PR), schon wenn die Metastasen eindimensional um 30% abgenommen haben... nur um einige dieser Versuche zu erwähnen. Soviel man weiss, war ein Teil der Vorschläge der CEOs an Präsident Trump etwa so: Man könnte die Medikamente während der ersten zwei Zyklen nicht in Rechnung stellen oder nur zu einem geringeren Preis als heute; wenn der Patient/die Patientin dann aber darauf anspricht, muss der volle Preis bezahlt werden. So ein Vorgehen würde erklären, warum die Zulassungskriterien einerseits viel lockerer gehandhabt werden sollen als heute, wo sie doch schon viel weniger rigoros sind als noch vor 20 Jahren! Anderseits wäre natürlich vorteilhaft, in vielen Situationen, in denen wir heute noch von *no change* sprechen, von einer partiellen Remission berichten zu können.
Fazit: Dieser Leitartikel der New York Times sollte unbedingt gelesen werden, und jedermann/frau sollte sich darüber Gedanken machen, da diese Entwicklung unweigerlich auch auf uns zukommt.

Franco Cavalli

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Flächendeckende und einheitliche Krebsregistrierung startet 2020

Ein wichtiges Ziel der Nationalen Strategie gegen Krebs (NSK) ist erreicht. Das Bundesgesetz über die Registrierung von Krebserkrankungen ist geschaffen – und die einheitliche und flächendeckende Krebsregistrierung wird 2020 eingeführt. Deren rechtliche Verankerung ist von grosser gesundheitspolitischer Bedeutung. Allerdings müssen in den Ausführungsbestimmungen und der Umsetzung der Krebsregistrierung Kompromisse eingegangen werden.

Die landesweite und einheitliche Erfassung aller Krebserkrankungen ist eine unentbehrliche Grundlage für eine wirkungsvolle Public-Health-Politik. Dank der Registrierung der epidemiologischen Daten zu Krebs können die Ursachen der Krankheit besser verstanden, präventive Massnahmen gezielter geplant und Rückschlüsse auf bestmögliche Therapien präziser gezogen werden. Mit dem neuen Bundesgesetz, welches im März 2016 vom Parlament verabschiedet wurde, wird die Registrierung von Krebserkrankungen gesetzlich verankert. Aus Sicht der NSK ist dies ein Erfolg und ein entscheidender Schritt in eine zukunftsweisende Patientenversorgung.

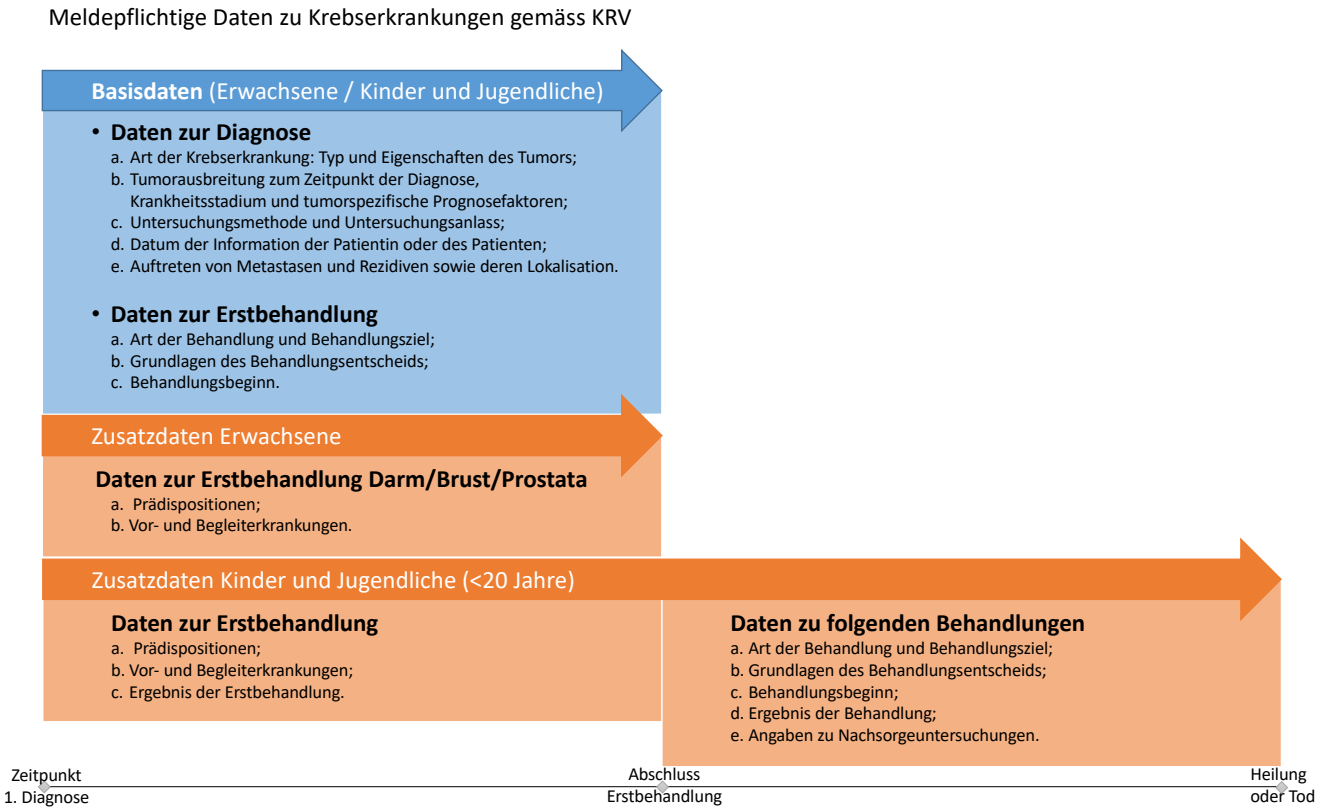
Basierend auf bestehendem System

Das Krebsregistrierungsgesetz (KRG) bestimmt die Rahmenbedingungen für die Erhebung, die Registrierung und die Auswertung von Daten zu Krebserkrankungen sowie von Daten zu anderen stark verbreiteten oder bösartigen nicht übertragbaren Krankheiten. Konkret sieht es die Einführung einer Meldepflicht von diagnostizierten Krebserkrankungen durch Ärztinnen und Ärzte, Spitäler sowie weitere private oder öffentliche Institutionen des Gesundheitswesens vor. Damit ist die Grundlage für eine vollständige und einheitliche Sammlung von Daten geschaffen. Zudem sind die Rahmenbedingungen zur Gewährleistung des Datenschutzes sowie das Widerspruchsrecht geregelt – Patientinnen und Patienten können der Registrierung ihrer Daten widersprechen.
Mit der Verordnung über die Registrierung von Krebserkrankungen (KRV) hat der Bundesrat im April 2018 die Bestimmungen für die Umsetzung des KRG verabschiedet. Gemäss der KRV baut die Registrierung der Krebserkrankungen auf dem bestehenden System auf. In kantonalen Krebsregistern – finanziert durch die Kantone – werden Daten zu Krebserkrankungen möglichst vollständig und vollzählig erfasst. Anschliessend werden auf nationaler Ebene die Daten durch die nationale Krebsregistrierungsstelle (NKRS) zusammengeführt und aufbereitet. Im Rahmen eines Ausschreibungsverfahrens hat das Eidgenössische Departement des Innern (EDI) das Nationale Institut für Krebsepidemiologie und -registrierung NICER mit den Aufgaben der NKRS beauftragt. Die NKRS sorgt für die nötige Harmonisierung, Standardisierung und Analyse der Daten, und erstellt zusammen mit den zuständigen Fachstellen Gesundheitsberichterstattungen und Krebsstatistiken. Krebserkrankungen bei Kindern werden weiterhin zentral in einem Kinderkrebsregister erfasst. Mit dieser Aufgabe wurde das Schweizer Kinderkrebsregister (SKKR) vom EDI betraut.

Basis- und Zusatzdaten

Bei jeder Krebserkrankung sollen künftig einheitliche Basisdaten erfasst werden. Dazu gehören diagnostische Daten sowie die Art, das Ziel und der Beginn der Erstbehandlung sowie die Grundlagen des Behandlungsentscheids. Zusätzlich werden sogenannte Zusatzdaten bei Erwachsenen für die drei am häufigsten auftretenden Krebserkrankungen (Brust-, Prostata- und Darmkrebs) erfasst.
Diese umfassen Angaben zu Prädispositionen sowie allfällige Vor- und Begleiterkrankungen. Bei Kindern werden Zusatzdaten für alle Krebserkrankungen erfasst und auch das Ergebnis der Erstbehandlung sowie Daten zu weiteren Behandlungen und Nachsorge.

Der 2017 in die Vernehmlassung geschickte Entwurf der KRV sah einen umfassenden Satz an zu registrierenden Daten vor, beispielsweise auch die Erfassung von Zusatzdaten zu Lungenkrebs bei Erwachsenen. Es war geplant, dass das KRG am 1. Januar 2019 in Kraft tritt und damit bereits ab nächstem Jahr Krebserkrankungen in der Schweiz flächendeckend registriert würden. Aufgrund kritischer Rückmeldungen in der Vernehmlassung hat sich der Bundesrat für eine Verkleinerung des Datensatzes



Krebsliga Schweiz, F. Lenz, 17.04.2018

sowie die Verschiebung der Inkraftsetzung um ein Jahr entschieden. KRG und KRV treten deshalb erst am 1. Januar 2020 in Kraft. Geplant ist, dass die NKRS und das Kinderkrebsregister ab Herbst 2018 mit den Vollzugsvorbereitungsarbeiten starten. Es kam zu diesem Kompromiss, um den Registrierungsaufwand und damit die Kosten für die Kantone einzudämmen und mehr Zeit für den Vollzug zu haben.

Arbeit geht weiter

Dass die vollständige Registrierung erst ein Jahr später als ursprünglich geplant umgesetzt wird, ist zwar schade, aber nicht entscheidend, wenn im Übergangsjahr 2019 keine Datenlücke entsteht und die Finanzierung der laufenden Register sichergestellt ist. Die Kantone sollten die Vollzugsarbeiten nicht unterbrechen, es gilt, die gewonnene Zeit sinnvoll zu nutzen. So kann die zeitliche Verschiebung eine Chance sein, die Umsetzung der Krebsregistrierung in den Kantonen sowie die Datenlieferung der Meldestellen vollständig und in guter Qualität vorzubereiten und dann umzusetzen.

Gemäss dem KRG sollen die gesammelten Daten dazu dienen, «Grundlagen für Präventions- und Früherkennungsmassnahmen zu erarbeiten und deren Wirksamkeit zu überprüfen, die Versorgungs-, Diagnose- und Behandlungsqualität zu evaluieren sowie die Versorgungsplanung und die Forschung zu unterstützen». Inwiefern dies mit dem nun eingeschränkten Basis- und Zusatzdatensatzes möglich ist, wird von Experten infrage gestellt. Es ist daher möglich, dass sich in Zukunft eine Ausweitung des Datensatzes aufdrängt. Trotzdem ist die flächendeckende und einheitliche Krebsregistrierung ein Erfolg. Um die Ziele des Krebsregistrierungsgesetzes zu erreichen, sind vollzählige und qualitativ hochwertige Daten zur Diagnose, sowie zum Krankheits- und Therapieverlauf nötig. Deshalb werden in diesem Zusammenhang zwei Projekte in der NSK-Weiterführung umgesetzt. Im Rahmen des NSK Projekts 7.1 wird die Einführung des KRG sowie der Aufbau der NKRS begleitet. Im Weiteren werden von der Arbeitsgruppe «Zusatzdaten KRG/Behandlungsqualität» im Projekt 7.2 unter dem Lead von NICER und SGMO Vorschläge für konkret zu erfassende Behandlungsdaten und Qualitätsindikatoren erarbeitet. Damit soll die Versorgungs- und Behandlungsqualität evaluiert werden können, um zu einer optimalen Versorgung aller Krebsbetroffenen in der Schweiz beizutragen.

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Interprofessioneller sektorenübergreifender Behandlungspfad Kolorektalkarzinom – assoziiertes Projekt der NSK erreicht einen Meilenstein

Esther Kraft, lic.rer.oec., Dr. med. Jürg Nadig, Dr. med. Jürg Pfisterer und das Projektteam[1]

Im Rahmen des Pilotprojekts interprofessioneller sektorenübergreifender Behandlungspfad Kolorektalkarzinom haben 20 verschiedene Fachgesellschaften und Berufsgruppen die Grundlagen erarbeitet, damit alle Patientinnen und Patienten mit Kolorektalkarzinom eine qualitativ hochwertige, optimal koordinierte und den (inter-)nationalen evidenzbasierten Richtlinien entsprechende Versorgung erhalten.

Ausgangslage

Aufgrund der Spezialisierung und der Fortschritte in der Behandlung von Krankheiten sind immer mehr Fachleute in die Abklärungs- und Behandlungskette eingebunden. Patienten[2] werden deshalb während einer Krankheitsphase sequenziell oder parallel von verschiedenen medizinischen und anderen Fachpersonen behandelt. Diese orientieren sich an Richtlinien, welche idealerweise den Stand der Wissenschaft zusammenfassen. Um Patienten auf ihrem Weg kompetent zu begleiten und Doppelspurigkeiten sowie unnötige Behandlungsverzögerungen zu vermeiden, sind komplexe Behandlungsabläufe zu koordinieren.

Assoziiertes Projekt der Nationalen Strategie gegen Krebs (NSK)

Für die NSK ist die Erarbeitung von Patientenpfaden/Behandlungspfaden ein Kernelement. Bis anhin fehlten für die Schweiz Daten zum Aufwand der Erarbeitung sektorenübergreifender Behandlungspfade und zum Mehrwert ihrer Implementierung. Um diese Fragen zu beantworten, initiierte die SAQM im Jahr 2013 das Pilotprojekt «sektorenübergreifender Behandlungspfad Kolorektalkarzinom». Das Pilotprojekt ist als ein assoziiertes Projekt unter dem Handlungsfeld Patientenpfade/Qualitätsentwicklung in die NSK eingebettet.

Projektziele

Die Vertreter der 20 Organisationen, die in die Behandlung des CRC eingebunden sind, erarbeiteten gemeinsam die Grundlagen, welche gewährleisten, dass ein an einem Kolonkarzinom erkrankter Patient, unabhängig von seinem Wohnort in der Schweiz, eine qualitativ hochstehende, standardisierte und optimal koordinierte, auf anerkannten (inter-) nationalen Richtlinien basierende Therapie erhält.

Neben der inhaltlichen Erstellung des Behandlungspfads sollen der Aufwand für dessen Erstellung und der Mehrwert einer Implementierung eines sektorenübergreifenden Behandlungspfads erfasst und Erfahrungen zur interprofessionellen Zusammenarbeit gesammelt und analysiert werden.

Breite Abstützung

An der Erarbeitung und Verabschiedung des sektorenübergreifenden Behandlungspfads Kolorektalkarzinom beteiligten sich 20 in die Behandlung involvierte Fach-

1. Mitglieder des Projektteams: Jürg Pfisterer (Co-Projektleitung); Jürg Nadig (Co-Projektleitung), Esther Kraft (Co-Projektleitung); Varja Meyer (Co-Projektleitung bis 2016), Gieri Cathomas (Schweiz. Gesellschaft für Pathologie); Regula Capaul (Schweizerische Gesellschaft für Allgemeine Innere Medizin); Stephan Vorburger (Schweiz. Gesellschaft für Chirurgie); Peter Bauerfeind (Schweiz. Gesellschaft für Gastroenterologie); Florian Strasser (Schweiz. Gesellschaft für Palliative Medizin, Pflege und Begleitung); Felicitas Hitz (Schweizerische Gesellschaft für Medizinische Onkologie); Christoforos Stoupis (Schweiz. Gesellschaft für Radiologie); Stephan Eberhard (Oncoreha); Adrienne Imhof (Schweiz. Gesellschaft für Viszeralchirurgie); Judith Adler (Schweiz. Gesellschaft für Psychoonkologie); Annette Ringger (Schweiz. Gesellschaft für Allgemeinchirurgie und Traumatologie); Antonio Nocito (Schweiz. Gesellschaft für Viszeralchirurgie); Michael A. Patak (Schweiz. Gesellschaft für Radiologie); Niklaus Schäfer (Schweiz. Gesellschaft für Nuklearmedizin) Martin Hübner (Schweiz. Gesellschaft für Viszeralchirurgie); Frank Zimmermann (Schweiz. Gesellschaft für Radio-Onkologie SRO); Irène Bachmann-Mettler (Onkologiepflege Schweiz); Béatrice Lütolf (Physioswiss); Monica Rechsteiner (Schweiz. Verband dipl. Ernährungsberater/innen); Yvonne Fent (Schweiz. Vereinigung der StomatherapeutInnen SVS); Maya Zumstein-Shaha (Schweiz. Verein für Pflegewissenschaft VFP); Nadine Behnke (Schweiz. Gesellschaft f. Palliative Medizin, Pflege u. Begleitung); Jürg Bernhard (Schweiz. Gesellschaft für Psychoonkologie); Elisabeth Portmann (Schweiz. Fachverband Soziale Arbeit im Gesundheitswesen).
2. Zur besseren Lesbarkeit wird in der Regel die männliche Form verwendet; Frauen sind mitgemeint.

Oncoreha	Onkologiepflege Schweiz
Physioswiss	Schweiz. Fachverband Sozialarbeit in Spitälern SFSS
Schweiz. Gesellschaft für Chirurgie SGS	Schweiz. Gesellschaft für Gastroenterologie SGG
Schweiz. Gesellschaft für Medizinische Onkologie SGMO	Schweiz. Gesellschaft für Medizinische Genetik SGMG
Schweiz. Gesellschaft für Palliative Medizin, Pfege und Begleitung	Schweiz. Gesellschaft für Nuklearmedizin SGNM
Schweiz. Gesellschaft für Phatologie SGPath	Schweiz. Gesellschaft für Psychoonkologie SGPO
Schweiz. Gesellschaft für Radiologie SGR	Schweiz. Gesellschaft für Radio- Onkologie SRO
Schweiz. Gesellschaft für Viszeralchirurgie SGVC	Schweiz. Verband dipl. Ernährungsberater/innen HF/FH SVDE
Schweiz. Gesellschaft für Stomatherapeutinnen SVS	Schweiz. Verein für Pflegewissenschaft VFP

Tab 1. Übersicht beteiligte Berufsgruppen.

gesellschaften und Berufsgruppen (**Tab.** 1). Weil die Mitglieder des Projektteams[1] von den entsprechenden Berufsorganisationen offiziell delegiert wurden, war die fachliche und berufspolitische Verankerung des Pilotprojekts von Anfang an gewährleistet. An dieser Stelle ein grosses Dankeschön an die Mitglieder des Projektteams für ihren unermüdlichen Einsatz. Ohne sie wäre dieses Projekt nicht realisierbar gewesen.

Interprofessioneller sektorenübergreifender Behandlungspfad Kolorektalkarzinom – Methodik und Ergebnis

Das Projekt verfolgte einen multidisziplinären, strukturierten bottom-up-Ansatz. Alle Entscheidungen im Projektteam mit den 20 Organisationen erfolgten im Konsens. Das gesamte Projektmanagement unterlag einer kontinuierlichen Planung, da die SAQM und die 20 Organisationen mit diesem Projekt in der Schweiz und auch im internationalen Vergleich Neuland betraten.

Die 20 Organisationen haben die nachfolgenden Empfehlungen für das dreipfadige Behandlungspfad-Schema Kolorektalkarzinom verabschiedet (Quelle: *https://www.fmh.ch/files/pdf18/Schema_Behandlungspfad1.pdf*).

Jeder Abschnitt des Behandlungspfads ist mit verschiedenen Schlüsselinterventionen[3] hinterlegt, welche die 20 Organisationen in einem ersten Schritt für ihren eigenen Fachbereich festlegten. In einem zweiten Schritt einigten sich alle beteiligten Organisationen auf ein gemeinsames Schlüsselinterventionsset. Die Evidenz der gewählten Interventionen ist transparent aufgeführt. Da die Evidenz der Schlüsselinterventionen am besten in den Richtlinien des National Comprehensive Cancer Network (NCCN, www.nccn-org) dokumentiert ist, und diese Leitlinien regelmässig adaptiert werden, haben sich die 20 Organisationen im Laufe der Arbeiten auf die Guidelines CRC des NCCN als Basis für den Behandlungspfad festgelegt. Liegen jedoch von den Fachgesellschaften und Berufsgruppen anerkannte nationale Empfehlungen/Richtlinien vor, haben diese Vorrang vor den NCCN-Guidelines. Im vorliegenden Behandlungspfad-Schema (**Abb.** 1) sind bei jeder neuen Krankheitssituation die Grundelemente Diagnostik/Staging und die damit verbundenen Basisabklärungen erforderlich. Diese Grundlage erlaubt erst eine Gliederung in potentiell heilbare Stadien, wahrscheinlich nicht heilbare Stadien und Situationen am Lebensende als Voraussetzung für einen interdisziplinär erarbeiteten, situationsgerechten Behandlungsplan. Damit die interdisziplinären Fallbesprechungen (Tumorboards) den grösstmöglichen Nutzen erzielen können, sind für diese Minimalkriterien festgelegt worden.

Der Behandlungspfad dient als Qualitätssicherungs- und Qualitätsentwicklungsinstrument für eine multiprofessionelle evidenzbasierte Patientenbetreuung. Der Behandlungspfad gilt lediglich für den Regelfall und ist keine in jedem Einzelfall gültige Handlungsanweisung.

Die Gesamtkosten (inkl. der Arbeitsstunden der SAQM und der beteiligten Organisationen sowie der nicht vergüteteten Stunden der Projektteammitglieder) für Entwicklung und Verabschiedung des hier vorliegenden Behandlungspfads belaufen sich auf ca. CHF 700‘000. Dieser Aufwand wurde vollumfänglich von den beteiligten Leistungserbringer-Organisationen getragen.

3. Schlüsselintervention (key intervention): Die notwendigen Diagnose- oder Behandlungsschritte, um unabhängig vom Wohnort eine qualitativ hochstehende, standardisierte und optimal koordinierte, auf anerkannten (inter-) nationalen Guidelines basierende Behandlung zu erhalten.

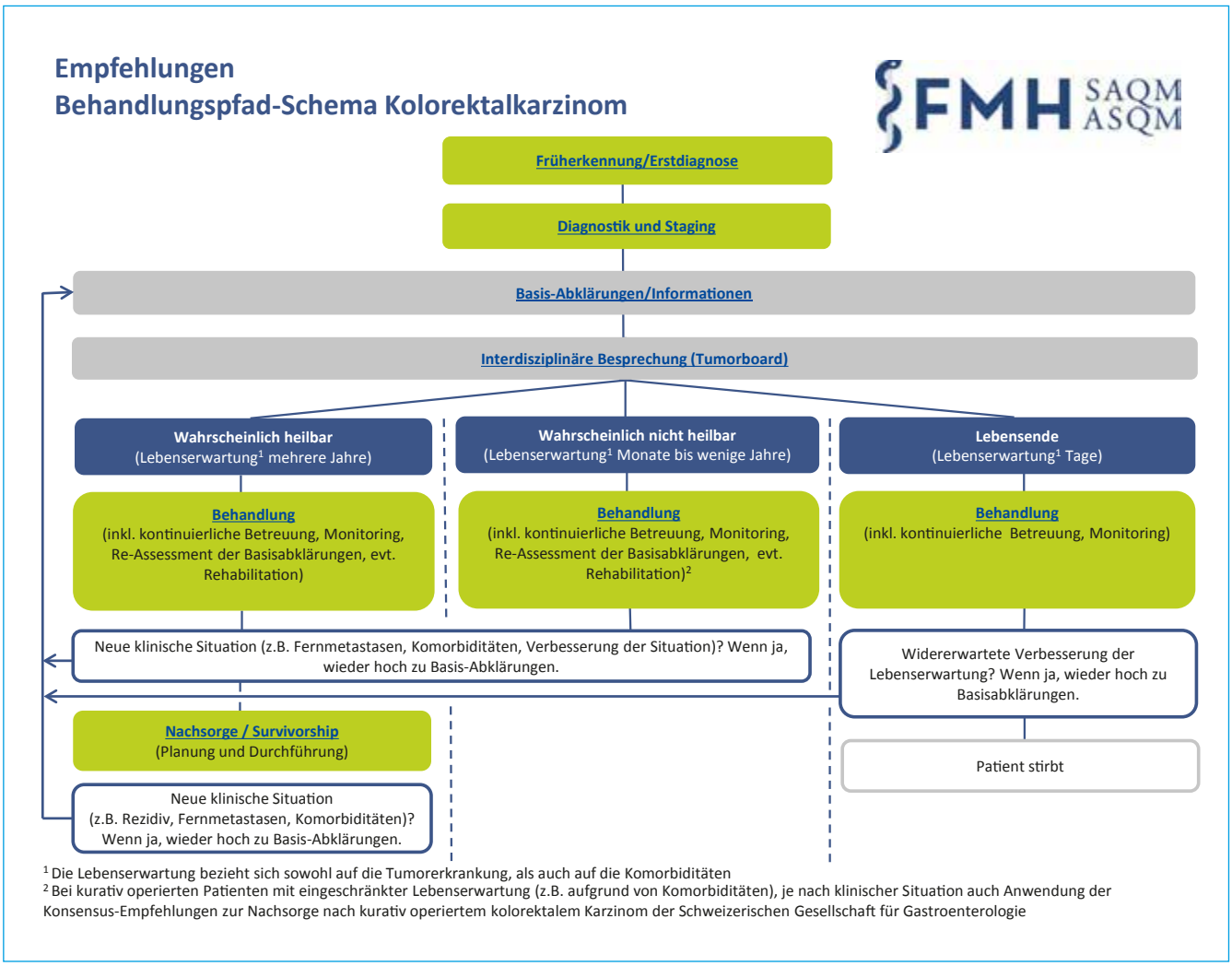

Abb. 1. Empfehlungen Behandlungspfad-Schema Kolorektalkarzinom.

Weiteres Vorgehen/Ausblick

Mit der Verabschiedung und Publikation des sektorenübergreifenden Behandlungspfads Kolorektalkarzinom ist der SAQM und den 20 beteiligten Organisationen ein erster Meilenstein gelungen, der auch auf internationale Beachtung gestossen ist. Als weiterer Projektschritt wird das vorliegende Behandlungspfad-Schema mit den hinterlegten Richtlinien und Empfehlungen regelmässig auf die Aktualität geprüft, evaluiert und angepasst.

Gleichzeitig ist das vorliegende Behandlungspfad-Schema in der täglichen Arbeit mit den Patientinnen und Patienten durch die ärztlichen und medizinisch-therapeutischen Leistungserbringer umzusetzen. Hierfür sind Pilotregionen zu definieren, in denen Aufwand und Mehrwert im Rahmen einer Begleitstudie erforscht werden. Die Resultate dieser Begleitforschung sind zentral für eine allfällige Erarbeitung weiterer Behandlungspfade.

Neben den Guidelines und Empfehlungen, die den Behandlungsstandard für die Leistungserbringer beschreiben, erarbeiten wir zusammen mit dem Dialog Ethik (unter Beizug internationaler Experten) Qualitätskriterien für Patienteninformationen, damit diese die Patienten bei ihrer Entscheidungsfindung unterstützen können. Die Qualitätskriterien werden im Verlauf des Herbst 2018 veröffentlicht.

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Die adjuvante Strahlentherapie beim nodal-negativen Mammakarzinom: ein individueller radioonkologischer Entscheidungsprozess

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Einleitung

Nach aktuellen Daten können wir von einer jährlichen Inzidenz des Mammakarzinoms in Europa von knapp unter 1% ausgehen und einem Risiko für Frauen von 9%, im Laufe ihres Lebens an Brustkrebs zu erkranken [1]. Da die Erkrankung in der Regel heilbar ist (jährliche Mortalität von 0,23%), zielen die Massnahmen in der Strahlentherapie neben der Verhinderung des Tumorrezidivs zunehmend auf einen Erhalt einer guten Lebensqualität ab. Erkenntnisse der letzten Jahre, unterstützt durch aktuelle Ergebnisse randomisierter Studien zur Wahl der Fraktionierung und des Zielgebietes der Strahlentherapie, eröffnen die Chance auf eine Deeskalation der Strahlentherapie [2], abhängig vom Vorliegen günstiger Risikofaktoren und der Berücksichtigung individueller Faktoren wie Tumorlage und -grösse, Brustform und -grösse und Wünsche der betroffenen Patientin [3-5].

Verzicht auf eine adjuvante Strahlentherapie

In den 80-iger Jahren wurden die ersten klinischen Studien veröffentlicht, die sich mit dem Verzicht auf eine Strahlentherapie bei brusterhaltendem Vorgehen befassten. Bei einer alleinigen adjuvanten endokrinen Therapie stieg die lokale Rezidivrate signifikant an, sodass in aktuelleren Studien auf eine bewusstere Selektion der Patientinnen geachtet wurde: Patientinnenalter, Hormonrezeptorstatus und Tumorgrösse wurden bei der Auswahl der Studienpatientinnen berücksichtigt (**Tab. 1**).

Aus den Studien können eindeutige Rückschlüsse auf die Bedeutung der adjuvanten Strahlentherapie für die lokale Tumorrezidivrate geschlossen werden: selbst bei kritisch selektionierter Auswahl der Patientinnen mit geringem Rezidivrisiko bleibt ein signifikanter Nutzen der Strahlentherapie hinsichtlich der lokalen Tumorkontrolle bestehen (Reduktion des absoluten Rezidivrisikos nach 5 Jahren von ca. 5% bei günstigem Risikoprofil) [5-7]. Aktuelle Simulationen von zukünftigen Studien belegen die Schwierigkeiten bei der richtigen Auswahl der Patientinnen, auch wenn moderne Parameter berücksichtigt werden (z.B. Oncotype) [8]. Bei strikter Beachtung der in die Modellrechnung eingehenden Kriterien kann allerdings ein Überlebensnachteil ausgeschlossen werden, solange eine regelmässige onkologische Nachsorge gesichert ist. Bei folgenden Faktoren erscheint der Verzicht auf eine Strahlentherapie demnach möglich [5, 9]:

- Tumorgrösse ≤ 2 cm
- Resektionsgrenzen > 2 mm
- Sehr begrenzte intraduktale Komponente
- Keine Lymphangiosis carcinomatosa
- Grading 1-2
- Östrogen- und Progesteronrezeptor positiver Tumor
- Unifokalität
- Patientinnenalter > 65 Jahre und Lebenserwartung unter 10 Jahre
- Endokrine Therapie wird durchgeführt

Die interdisziplinäre Entscheidung zum Verzicht auf eine Strahlentherapie sollte sorgfältig gegenüber dem alternativen Verzicht auf eine adjuvante endokrine Therapie abgewogen werden, da deren Durchführung aufgrund von Nebenwirkungen nicht immer konsequent möglich ist [4, 5, 10, 11]. Als Basis des Entscheides sollten auch geriatrische Assessments vorgenommen werden, um die tumorunabhängige Lebenserwartung der Patientin präziser einschätzen zu können.

Alleinige Strahlentherapie des Tumorbettes

Die Mehrzahl der lokoregionären Rezidive nach alleiniger Operation tritt ohne weitere Massnahmen im Tumorbett auf. Zur Klärung der Effektivität einer alleinigen lokalen Strahlentherapie des Tumorbettes wurden randomisierte Studien mit unterschiedlichen Bestrahlungstechniken durchgeführt, nach deren Ergebnissen Kriterien für eine mögliche Indikation zur ausschliesslichen Teilbrustbestrahlung festgelegt wurden [12, 13]. Die nachfolgenden Kriterien stellen die konsequenteste Schnittmenge der Forderungen dar [14]:

- Alter der Patientin ≥ 60 Jahre
- Invasiv-ductales Karzinom
- Tumorgrösse ≤ 2 cm
- Tumorfreier Resektionsrand > 2 mm
- Kein tumorbefallener Lymphknoten (pN0)
- Keine Lymphangiosis (L0)
- Hormonrezeptor-positiver Tumor
- Grading 1 oder 2
- Tumor unizentrisch und unifokal
- Kein begleitendes ausgedehntes ductales Carcinoma in situ (DCIS)
- Keine BRCA 1 / 2-Mutationen
- Keine Indikation zur Chemotherapie

Studie	Jahre	Patienten	Tumor	Nachbeobachtung (Jahre)	Therapie	Lokalrezidiv (%)
NSABP B-21	1989-1998	1009	pT1 (< 1 cm) pN0	7,2	Tam RT Tam + RT	16,5 9,3 2,8
Deutsche Studie	1991-1998	347	pT1pN0, ER+, G 1-2 Alter 45-70 Jahre	10,0	Tam RT Tam + RT	34 10 5
Britische BASO II-Studie	1992-2000	406	pT1pN0, G 1, L0 Alter < 70 Jahre	10,0	Keine Therapie Tam RT RT Tam + RT	17 7 7 0
Kanadische Studie	1992-2000	769	pT1-3, Alter < 50 Jahre	5,6	Tam Tam + RT	7,7 0,6
GALGB 9343	1994-1999	636	pT1pN0, ER+ Alter ≥ 70 Jahre	12,6	Tam Tam + RT	10,0 2,0
ABCSG 8A	1996-2004	869	pT1-2pN0, G 1-2, ER+	4,5	Endokrin Endokrin + RT	5,1 0,4
Italienische Studie	2001-2005	749	pT1-2 (<2,5 cm) Alter 55-75 Jahre	9,0	Endokrin Endokrin + RT	4,4 3,4
PRIME II	2003-2009	1326	pT1-2, G3 oder L1 Alter ≥ 65 Jahre	5,0	Endokrin Endokrin + RT	4,1 1,3

Tab. 1. Übersicht randomisierter Studien zum Verzicht auf eine adjuvante Strahlentherapie im Rahmen des brusterhaltenden operativen Vorgehens mit adjuvanter endokriner Therapie (Tam = Tamoxifen; RT = Strahlentherapie; ER+ = positiver Hormonrezeptorstatus; endokrin = endokrine Therapie mit Tamoxifen bzw. Anastrozol) [5].

Derzeit stehen folgende Techniken für eine Strahlentherapie des Tumorbettes bzw. des betroffenen Quadranten während des oder zügig nach dem operativen Eingriff zur Verfügung:

- Intraoperative Elektronenbestrahlung (IOERT): mittels eines (teilweise mobilen) Linearbeschleunigers (Mobetron®, Novac 7® oder LIAC®) im Operationssaal (mit Zusatzausstattung hinsichtlich des Strahlenschutzes) oder im herkömmlichen Bestrahlungsraum mit vorherigem Transport der Patientin dorthin [15];
- IntraBeam®: mittels eines mobilen kV-Röntgentherapiegeräts nach intraoperativer Platzierung eines in der Größe passenden Tubus im Tumorbett, im üblichen Operationssaal (weltweit homogener Einsatz von 1 x 20 Gy über ca. 25 Minuten, je nach Tubusgrösse) [15];
- MammoSite®, SAVI® oder Contura®: über einen intraoperativ im Tumorbett platzierten Ballon, der über einen oder mehrere Katheter in Afterloadingtechnik im eigenen Bestrahlungsraum kurz nach der Operation über 2 bis 4 Tage in mehreren Sitzungen beschickt wird [15];
- Interstitielle Brachytherapie: mittels intraoperativ oder postoperativ platzierter Kunststoffkatheter, in die die Strahlenquelle per Afterloadingtechnik über mehrere Tage in den Tagen nach der Operation gebracht wird, im eigenen Bestrahlungsraum (weltweit variable Fraktionierungsschemata und Therapieplanungen, z.B. 8 x 4 Gy in 4 Tagen) [13];
- Perkutane Strahlentherapie mit Photonen oder Elektronen: mittels Linearbeschleuniger nach der Operation als CT-geplante Therapie, in der Regel über maximal 2 Wochen mit ein bis zwei Behandlungen pro Tag, beginnend ca. 4 Wochen nach der Operation (weltweit variable Fraktionierungsschemata, z.B. als dynamische intensitätsmodulierte Strahlentherapie mit 10 x 3,85 Gy in 5 Tagen) [15].

Diese Verfahren der Teilbrustbestrahlung unterscheiden sich in Hinblick auf den zeitlichen Aufwand der Therapie, die benötigte Erfahrung des Therapeuten, die Grösse und Variabilität des behandelbaren Zielgebietes und den benötigten Aufwand hinsichtlich des Strahlenschutzes und damit der Investitionskosten. Nachteil der bereits intraoperativ eingesetzten Teilbrustbestrahlungen ist vor allem das Fehlen des endgültigen histopathologischen Ergebnisses [5, 16]. In bis zu 22% der Patientinnen musste daher in Studien noch eine postoperative Strahlentherapie der gesamten Brust durchgeführt werden, da sich im

endgültigen Ergebnis tumorbedingte Risikofaktoren für einen subklinischen Befall jenseits der Resektionsränder fanden. Die bessere Schonung gesunder Gewebe (u.a. Herz) konnte in allen Studien bestätigt werden, nicht jedoch die Hoffnungen auf ein besseres kosmetisches Ergebnis [17]. Bei Tumoren mit niedrigem Risikoprofil ist die alleinige Strahlentherapie des Tumorbettes mittlerweile aufgrund der guten 5-Jahresüberlebensraten etabliert.

Perkutane Strahlentherapie der gesamten Brust

In den letzten Jahren wurden die Ergebnisse mehrerer multizentrischer randomisierter Phase-III-Studien publiziert, die zu einem Wechsel im Fraktionierungskonzept der adjuvanten Strahlentherapie der gesamten Brust geführt haben. Die Einzeldosen wurden erhöht (anstelle von 1,8 - 2,0 Gy auf mehr als 2,5 Gy pro Tag) bei gleichzeitiger Reduktion der Gesamtdosis, um den strahlenbiologischen Effekt der erhöhten Einzeldosis zu berücksichtigen: biologisch ähnliche Effekte waren nach Modellrechnungen von 50 Gy Gesamtdosis (bei 5 x 2,0 Gy pro Woche) und von 40 Gy Gesamtdosis (bei 4 bis 5 x 2,67 Gy pro Woche) zu erwarten. Zahlreiche randomisierte Studien mit nunmehr über 10 Jahren Nachbeobachtung (siehe **Tab. 2**) haben die Erwartungen belegen können: eine gute Verträglichkeit der Therapie, auch hinsichtlich der Lebensqualität und der funktionellen Ergebnisse, und die mindestens gleich geringen Rezidivraten wie bei den herkömmlichen Fraktionierungsschemata [18].

Die Ergebnisse der unten genannten Studien können wegen geringer Subgruppengrösse nicht uneingeschränkt auf folgende Situationen übertragen werden:

- Patientinnenalter unter 50 Jahren
- Patientinnen mit sehr grosser Brust und ungünstiger inhomogener Dosisverteilung
- Einschluss der regionalen Lymphbahnen in das Bestrahlungsvolumen
- Strahlentherapie nach Einlage von Expandern oder grösseren plastisch-rekonstruktiven Verfahren
- Situation nach neoadjuvanter Chemotherapie
- Durchführung einer zeitgleichen Behandlung mit Trastuzumab.

In diesen Fällen sollte die individuelle Entscheidung zum Vorgehen sorgfältig abgewogen werden.

Dosiseskalation (Boost) im Tumorbett

Bei lokal fortgeschrittenen Mammakarzinomen konnten durch die Einführung einer postoperativen Strahlentherapie mit Dosiseskalationen im Bereich des Tumorbettes mit bis zu zusätzlichen 26 Gy mindestens vergleichbare, wenn nicht sogar bessere Überlebensraten als bei radikalem operativen Vorgehen (Mastektomie) erreicht werden [19, 20]. Systematische Analysen und aktuelle Langzeitergebnisse der Studien zeigen den Nachteil einer Dosissteigerung von mehr als 16 Gy auf (EORTC-Studie 10801: klinisch erkennbare Fibroserate von mehr als 30% bei 26 Gy Boost). Konsequenz einer Interimsanalyse der Studiendaten war daher die Reduktion der Boostdosis auf 16 Gy und die Klärung, in welcher Situation vollständig auf den Boost verzichtet werden könnte (EORTC

Studie	Jahre	Patienten	Nachbeobachtung (Jahre)	Stadien	Fraktionierungsschemata (Gy)*	Lokalrezidiv (%)
Royal Marsden	1986-1998	1410	9,7	T1-T3N1	25 x 2,0 13 x 3,3 13 x 3,0 (in 5 Wochen)	12,1 9,6 14,8
Ontario Group	1993-1996	1234	12	T1-2N0	25 x 2,0 16 x 2,66	6,7 6,2
Britische START-A	1999-2002	2236	9,3	T1-3aN0-1	25 x 2,0 13 x 3,0 13 x 3,2 (in 5 Wochen)	6,7 8,1 5,6
Britische START-B	1999-2001	2215	10	T1-3aN0-1	25 x 2,0 15 x 2,66	5,2 3,8
MD Anderson	2011-2014	287	2,2	Tis-T2N0	25 x 2,0 16 x 2,66	

Tab. 2. Randomisierte Studien zur adjuvanten hypofraktionierten Strahlentherapie des Mammakarzinoms.
*bei Vorliegen von Risikofaktoren erfolgte eine Dosissteigerung im Tumorbett (Boost) in allen Studienarmen mit Ausnahme der Ontariostudie [15].

22881). Aufgrund der Reduktion der Boostdosis kam es in der Gruppe, die einen Boost erhielt, nur zu einer Zunahme der schweren Fibrose von 3,4% [21], belegt also die grundsätzlich gute Verträglichkeit der Therapie.

Ein Nutzen des Boostes ergibt sich nach der EORTC-Studie nach einer gemeinsamen Auswertung mit Daten dänischer Register und auf der Basis aktueller Reviews [22, 23] vor allem bei Patientinnen unter 40 Jahren (Verbesserung der lokalen Kontrolle nach 20 Jahren um 11,6% gegenüber lediglich 3,0% bei Patientinnen über 60 Jahren) und bei begleitender extensiver intraduktaler Komponente. Ca. 50% der Rezidive traten im ehemaligen Tumorbett und im Bereich der Operationsnarbe auf. Die aktuellen Daten belegen die Möglichkeit eines Verzichtes auf den Tumorboost für ausgewählte Patientengruppen, da der Nutzen auf unter 5% hinsichtlich der lokalen Tumorkontrolle fällt und sich keine Nachteile hinsichtlich des Überlebens aufgrund der Möglichkeiten einer nachfolgenden Mastektomie ergeben: bei älteren Patientinnen (> 60 Jahre) mit kleinem Tumor (pT1), guter Differenzierung (G1-2) und sicher tumorfreien Resektionsrändern. In den 5-Jahresergebnissen einer nachfolgenden Studie mit höherer Boostdosis für Patientinnen unter 51 Jahren (Young Boost Trial) bestätigt sich hingegen die Notwendigkeit einer Dosiseskalation des Boostes für diese Subgruppe [21]. Somit ist bei Vorliegen von zusätzlichen Risikofaktoren (Alter unter 50 Jahre, begleitende intraduktale Komponente und R1-Status) auch ohne Langzeitergebnisse eine Eskalation des Dosisboostes auf mindestens 20 Gy bei positiven Schnitträndern vertretbar.

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Oligometastatic Disease

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In recent years, the concept of «oligometastatic» disease has started to change the treatment paradigm of patients with only few («oligo» in greek) metastases.

The concept itself was introduced by Hellman and Weichselbaum as early as 1995 and describes an intermediate stage between purely localized and widely metastatic disease. They hypothesize that there is a stage in the disease progression in which the ability for metastatic spread has not been fully developed yet, therefore opening up a time window in which a curative treatment is still possible [1, 2].

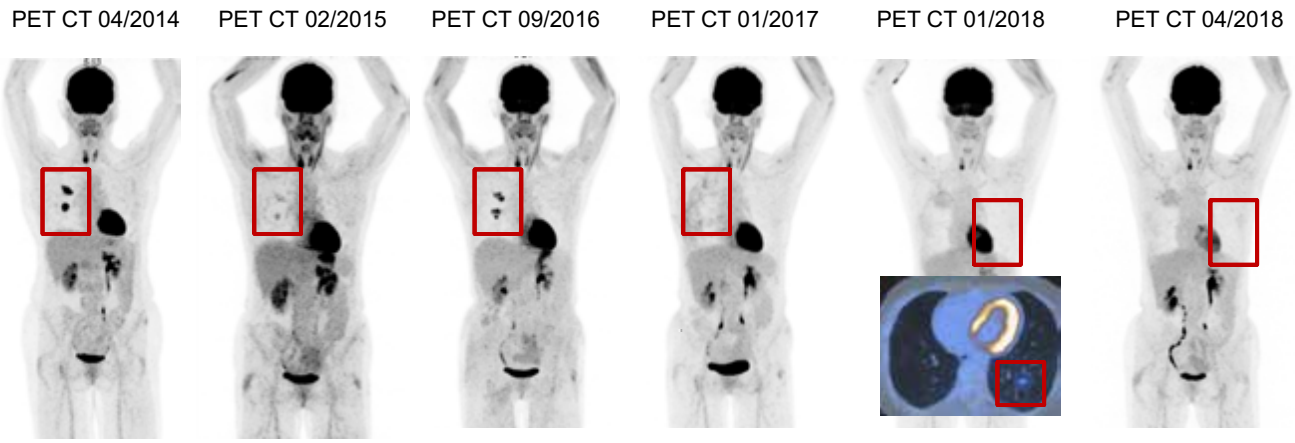
Early on this concept was supported by evidence of a good disease-free and overall-survival, most prominently after surgical resection of liver metastases in patients with colorectal carcinoma or lung metastases in patients with soft tissue sarcoma [3-6]. Generally, the therapeutic options are not limited to surgery alone, but include numerous locally ablative therapies including radiation therapy.

With the development of precise and locally highly effective techniques, like stereotactic body radiation therapy (SBRT), radiation therapy is one of the main treatment modalities in this group of patients [7].

Nowadays, the concept of oligometastatic disease is more and more integrated into the clinical routine when treating patients with only a few metastases and favourable prognosis though generally, there is limited evidence regarding both, the amount and the quality of existing publications. However, there is an increasing evidence for some tumor entities, including non-small cell lung cancer (NSCLC), prostate cancer and colorectal cancer.

One of the first groups of patients, in which the concept of oligometastatic disease and the radical local treatment of metastatic sites was described, were those with colorectal carcinoma suffering from liver metastases. In these patients, resection of liver metastases led to a favorable disease

59 year old patient with NSCLC of the right lower lobe and metastasis of a right rib (first diagnosis 04/14) – Systemic therapy with Erlotinib/Bevacicumab from 06/2014



free survival. Giacchetti et al. for instance reported a 25% 5-year disease-free survival after resection for metastatic colorectal carcinoma [8]. Pitroda et al. classified patients with colorectal liver metastases according to molecular subtypes combined with a clinical risk score. They identified three subtypes (low, intermediate and high risk) with an excellent 10-year OS of up to 94% in the low risk group [9].

A randomized controlled approach was published by Ruers et al. (CLOCC trial) in 2012 and was updated in 2017. In this trial the overall-survival (OS) of 119 patients without extrahepatic disease was evaluated after either systemic therapy alone or systemic treatment plus locally ablative treatment using radio-frequency ablation. After a median follow-up time of 4.4 years a significantly improved progression-free survival (PFS) in the combination arm (hazard ratio (HR) 0.63, p = 0.025) was shown, which did not yet translate into a significantly better overall-survival HR 0.74, p = 0.218) [10]. The long-term follow-up data published in 2017 now also shows a statistically significant OS benefit (HR 0.58, P = 0.01) at almost 10 years follow-up for patients in the combination arm. The OS-rate at eight years was 35.9% vs. 8.9% for the combined therapy arm and the systemic treatment only arm, respectively [11].

The promising data of aggressive local treatment in oligometastatic patients with colorectal carcinoma is also reflected in the ESMO guidelines featuring a passage on oligometastatic disease [12]. It is emphasized that in metastatic patients systemic therapy is still the standard of care and should be considered as the initial part of the treatment strategy, with the exception of patients with only a few liver or lung lesions. In these patients an ablative local treatment should be considered. They offer a toolbox of different ablative therapies, including stereotactic body radiotherapy (SBRT) if the preferred surgical resection is not possible.

Likewise, for non-small-cell lung cancer (NSCLC) the concept of oligometastatic disease was implemented into the 8th version of the TNM system and the NCCN guidelines as well as the ESMO guidelines. Stage IVa M1b is defined as a single extrathoracic metastasis, where local treatment with radiotherapy or surgical resection is recommended [13]. The recommendations in the ESMO guidelines are more cautious: it is stated that oligometastatic patients may experience a good disease-free survival following systemic therapy and radical local treatment but that due to the limited high-level evidence the inclusion in clinical trials is recommended. An exception are patients with brain metastases, for whom a radical local treatment with surgical resection and/or stereotactic radiotherapy is recommended [14].

Currently, the published data of two prospective randomized trials by Gomez et al. and Iyengar et al. are available. Though there are differences in the design of the trials and small sample sizes, both trials showed a significantly better PFS in patients treated with a combination of local ablative radiotherapy and systemic therapy vs. systemic therapy alone [15, 16].

Prostate cancer patients constitute another group for which the concept of oligometastatic disease is commonly used. Though the general problem of low level evidence also applies here, there is data, mostly retrospective, but also some from prospective randomized trials supporting radical local treatment like prostatectomy or SBRT for patients with metastatic disease.

Regarding cytoreductive prostatectomy in patients with metastatic disease, Heidenreich et al. and Gratzke et al. found it to be feasible and observed a better OS than in patients without a local resection. Additionally, patients treated with a surgical resection experienced no cancer-related symptoms like those without a local treatment [17, 18].

O`Shaughnessy et al. described a small series of 20 patients receiving multimodal therapy including Androgen Deprivation Therapy (ADT), radical prostatectomy and SBRT on bone metastases or primary site in oligometastatic setting. 95% of patients achieved an undetectable PSA of which 20% remained undetectable following testosterone recovery for up to 46 months [19].

One of the best quality data regarding locally ablative therapy on metastases using SBRT in metastatic prostate cancer was published by Ost et al. In 2016, they published the results of a retrospective multicenter analysis including 119 patients with up to three N1 or M1a-c lesions after primary locally ablative therapy for prostate cancer. They found it to be safe and observed prolonged progression free interval as well as a meaningful period without ADT [20]. Just recently in February of this year the authors elaborated on this in terms of a phase II prospective randomized trial including 62 patients with ≤ 3 metastases. Patients were randomly assigned to either surveillance or metastasis-directed therapy (surgery or SBRT). The patients in the therapy group showed a better ADT-free survival, though the results were not significant. Generally, the treatment was well tolerated without any ≥ grade 2 toxicities. Although these results are promising, the authors emphasized the need for phase III trials in their conclusion, further re-enforcing the need for high-level evidence on the subject [21].

Up to this day both the definition of an oligometastastic disease and the selection of patients for a locally curative

treatment remains challenging. In the initial publication from 1995, Hellmann and Weichselbaum already emphasized the importance of the identification of the intermediate tumor stage, the oligometastatic disease. 20 years later, Reyes and Pienta examined 20 clinical studies on oligometastatic lung cancer, found 17 different definitions of oligometastatic disease and each study performed a different treatment protocol [22]. Still, up to this day the implementation of prospective trials with a sufficient number of patients remains challenging. An opportunity to pool existing data regarding treatment schemes, outcome and toxicity profile lies in the implementation of register trials [23]. The accumulation of clinical data could enable safe and beneficial standards of care. The clinic for radiation oncology of the University Hospital Zürich has a leading role in two of these trials, the TOaSTT (Toxicity and efficacy of combined stereotactic radiotherapy (SRT) and systemic targeted or immunotherapy) trial and joint Oligocare project of the EORTC and ESTRO. Both of these will hopefully help to further improve patient care on a daily clinical basis.

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Radiation Therapy to Harness the Immune System in the Era of Cancer Immunology

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Introduction

Over the past decade, immunotherapy (IMT) treatments that function by driving the immune system to fight cancer, have emerged as a game changer in oncology. However, while immune checkpoint blockade (ICB), for example, has shown remarkable clinical responses against a variety of tumors, the proportion of patients obtaining clinical benefit when used as single modality is relatively low, at only 15-20% [1, 2]. Thus, there is an urgent need to develop novel combinatorial regimens that increase response rates to IMT.

A prerequisite for response to ICB is the presence of tumor infiltrating lymphocytes (TILs) in the tumor microenvironment (TME) [3-6]. In the context of infiltrated «hot» tumors, ICB, such as antagonists of the program death 1/ligand 1 (PD1/PDL1) axis, reinvigorate the activity of pre-existing antitumor T cells [6, 7]. Tumors that lack immune infiltration, so-called «cold» tumors, are refractory to ICB. Radiation therapy (RT) is a widely used anticancer treatment, and has undergone significant technological improvements that can guarantee the precise delivery of x-rays with limited and manageable side effects [8]. In preclinical tumor models robust systemic immune responses have been observed when RT is combined with ICB. Moreover, anecdotic cases of «abscopal effects», the disappearance of unirradiated tumor deposits when other metastases are irradiated, have been described [9, 10]. Thus, RT has the potential to be broadly used as a powerful and safe approach to convert «cold» or T-cell «excluded» tumors into inflamed ones [11]. Here we review the main mechanisms by which RT can elicit tumor immunity [12], *in situ* vaccination and immune reprogramming, and we provide examples of pharmacological interventions that boost abscopal responses in current immuno-oncology practice.

Intratumoral *in situ* vaccination induced by radiation therapy

The damage caused to proliferating tumor cells following exposure to radiation initiates a variety of transcriptional responses that may alter cell-cycle progression, induce DNA repair, and/or trigger cell death. Single strand breaks (SSBs) and double strand breaks (DSBs) induced by RT are sensed by proteins that activate the expression of surveillance genes, including p53, ATM, and DNA-protein kinase, which initiate cell-cycle arrest to allow repair of DNA, either by homologous recombination or by non-homologous end-joining pathways [13, 14]. DNA damage that cannot be adequately repaired signals through ATM and p53 to initiate apoptosis *via* the mitochondrial pathway [13, 15]. Within hours after radiation exposure, cells produce a range of factors including cytokines, chemokines, cell surface receptors, adhesion molecules, and enzymes, that co-ordinate tissue responses to RT. Additionally, the dying tumor cells may release danger signals that will ignite an inflammatory reaction, a so-called immunogenic death, *i.e.* cell death that effectively exposes tumor antigen and triggers an antitumor immune response. Three important hallmarks of immunogenic cell death, illustrated in **Figure 1**, include:

1. The translocation of calreticulin (CRT) from the endoplasmic reticulum to the cell surface: CRT acts as an «eat me» signal promoting antigen capture and presentation by dendritic cells (DC), releasing cytokines such as IL-6 and TNF-α, and stimulating specific anti-tumor T-cell responses [16].
2. The release of high-mobility group box 1 (HMGB1): HMGB1 is an abundant chromatin nuclear protein that is released mainly after necrotic cell death and that interacts with TLR ligands on antigen presenting cells (APC). The redox state of this protein may determine whether it promotes immunogenicity or tolerance [17-21].
3. The release of adenosine triphosphate (ATP): ATP acts as a «find-me» signal for monocytes and DCs [22-24], leading to the secretion of pro-inflammatory cytokines such as IL-1β and IL-18 [25].

In addition, tumor cells that receive RT undergo phenotypic changes that enhance their susceptibility to be eliminated by the immune system. Complement anaphyl-

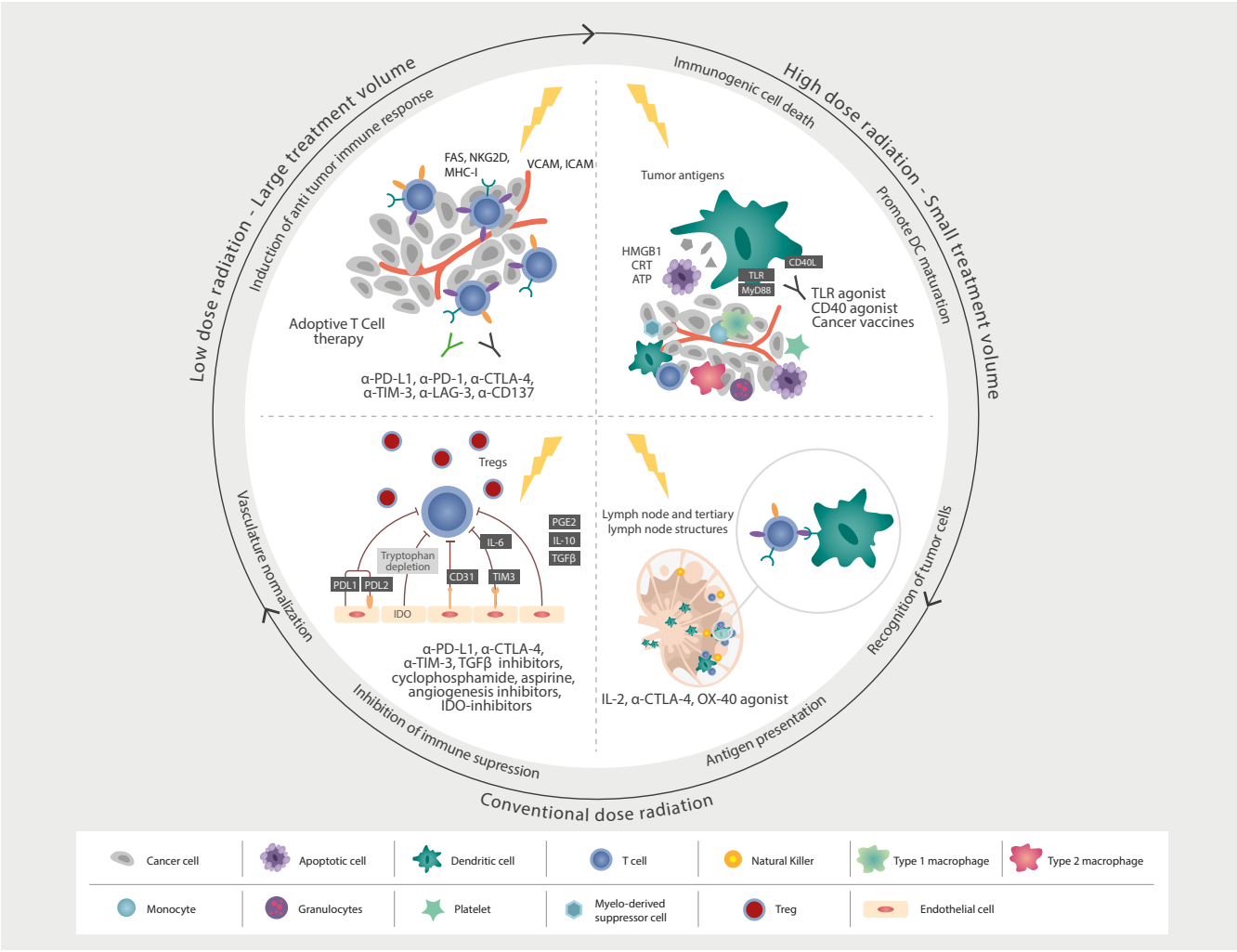

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Fig. 1. Ionizing radiation acts as a modifier of the tumor microenvironment providing multiple elements for the tumor to serve as an *in situ* autologous vaccine. The cascade of immune-events induced by radiation provides a wide range of potential therapeutic targets to increase responses to cancer immunotherapy. Examples of immunotherapy strategies that have the potential to synergize with radiation therapy at each step of these immune-events are highlighted. I) Radiation induces immunogenic cell death of tumor cells characterized by calreticulin translocation to the surface of dying tumor cells, and release of HMGB-1 and ATP. Calreticulin allows uptake of dying cells by dendritic cells. HMGB-1 binds to TLR4 on dendritic cells and promotes the cross-presentation of tumor antigens, while ATP binds to P2X7 and triggers the activation of the inflammasome. Key synergistic combinatorial strategies at this step include vaccines, CD40 agonists, and TLR agonists. II) Activated dendritic cells migrate to the draining lymph node, where they activate naïve T cells specific for tumor antigens. Combination of radiation with IL2, CTLA-4 blockade, OX40 agonist could be of help to increase priming and activation of T cells. Activated antigen-specific CD8 T cells that acquire effector functions traffic to the tumor guided by radiation-induced chemokines, and infiltrate the irradiated and non-irradiated tumors (abscopal sites). III) However, the immunosuppressive tumor microenvironment coupled with the immune regulatory feedback mechanisms induced by radiation itself will halt the development of an appropriate immune response. Antibodies against PD1/PDL1, IDO, and TGFβ as well as anti-angiogenic treatments, could be of help at this step to eliminate barriers for T cell infiltration in tumors. IV) Tumor infiltration by cytotoxic T cells is facilitated by radiation-induced upregulation of VCAM-1 on the vascular endothelium. Once in the tumor, cytotoxic T cells interact efficiently with tumor cells expressing increased levels of MHC-I, ICAM-1, NKG2D ligands, and Fas that promote the formation of stable immunological synapses between targets and effectors and facilitate the killing of tumor cells by cytoxic T cells. The release of additional tumor antigens in an inflamed tumor context feeds forward this «virtuous» tumor immunity cycle. At this step adoptive T cell therapy or drugs that fuel the process like CTLA-4 and PD1/L1 could help to reduce T cell exhaustion in the tumor microenvironment.

atoxins, released following complement activation by RT-induced immunoglobulin M (IgM) binding to necrotic tumor cells, may directly contribute to DC recruitment and maturation, and ultimately to T cell immunity [26]. Induction of NKG2D receptor ligands upon irradiation mediates activation of NK cells, γδ T cells, NKT cells, and memory and activated CD8+ T cells [27, 28]. RT can also upregulate the expression of the FAS death receptor on tumor cells which induces the activation of cytotoxic T cells via FAS ligand expressed on their surface [29]. Further, RT upregulates major histocompatibility complex (MHC) class I molecules on tumor cells enabling enhanced direct presentation of tumor-associated antigens (TAA) [30], and it induces cGas-STING, a cytosol DNA damage sensing pathway that culminates in the induction of type I interferon (IFN) gamma and adaptive immune responses [31].

Immune reprogramming by radiation therapy

Many of the TME responses to RT exposure can either directly or indirectly attract and/or activate cytotoxic T cells, thus bearing the potential for turning a cold and non-inflamed tumor into a hot one that is responsive to IMT. For example, pro-inflammatory cytokines induced by RT, including IL1β, tumor TNF-α and type 1 and 2 IFNs [32, 33], act as paracrine signals to attract and activate APCs that cross-present tumor antigens and prime T lymphocytes. And CXCL16, which has been shown to be induced by RT (*via* IFN-γ and TNF-α), promotes the recruitment of effector CD8+ and T-helper 1 CD4+ T cells [34, 35]. In addition to providing chemo-attractants to recruit T cells, RT can also facilitate their migration into the tumor bed via the upregulation of adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1) on the tumor vasculature endothelium [36, 37], that assists leukocyte endothelial transmigration [29, 38, 39].

Some effects of RT on the TME, however, may have a negative impact on immunity. For example, RT can increase the recruitment of myeloid derived suppressor cells (MDSCs) which promote blood vessel formation and tumor regrowth [40]. Tumor associated macrophages (TAMs), which are typically M2, have also been implicated in the promotion of angiogenesis, tumor growth and metastasis following RT [41, 42]. These express the anti-inflammatory cytokines IL-10 and transforming growth factor beta (TGFβ), as well as the enzyme arginase-1 (which depletes extracellular L-arginine), which cause T cell suppression [43]. Through the upregulation of TGFβ, RT also leads to the recruitment of suppressive Foxp3+ T regulatory cells (Tregs) [44, 45]. In addition, TGFβ can promote extracellular matrix production and angiogenesis [46], enabling tumor cell proliferation, adhesion and metastasis [47].

The cascade of immune inhibitory events in the TME following radiation exposure are part of a homeostatic repair mechanism triggered to promote normal tissue recovery that unfortunately attenuates the immunomodulatory and tumor cell killing capacity of RT [48, 49]. Counteractive measures, however, can be taken. For example, in pre-clinical glioblastoma models, the inhibition of MDSCs by blocking CSF1 increased sensitivity to RT [40, 50, 51]. Similarly, inhibition of M2 macrophages before RT conferred protection from radiation induced tissue damage [52, 53]. Further, the deleterious effect of TGFβ could be reverted in a murine breast cancer model by combining RT (5x6 Gy) with TGFβ blockade and PDL-1 blockade [54]. As a final example, the use of low-dose irradiation (0.5-2 Gy) was shown to effectively convert M2 macrophages into an M1 phenotype in a murine pancreatic cancer model, and to synergize with adoptively transferred T lymphocytes for tumor control [11]. In summary, although radiation can potently promote the recruitment and activation of DCs and cyotoxic T cells through a variety of mechanisms, this may be counteracted by the concomitant migration of suppressive immune cells. There is thus tremendous opportunity for combining RT with immuno-modulatory agents for improved tumor control.

Abscopal responses to RT

Although the abscopal effect has been reported over many years, its occurrence had been rare until combination with immune modulators that either indirectly or directly promote T cell function. In a murine breast cancer model, for example, treatment with RT (either at a single dose of 2 Gy or a single dose of 6 Gy) on one flank combined with systemic delivery of FMS-like tyrosine kinase receptor 3 ligand (FLT3L), a potent cytokine that promotes DC maturation, led to a significant growth delay of both the irradiated and non-irradiated tumors, and the abscopal effect was shown to be dependent on the presence of T cells [55]. More recently, investigators reported abscopal effects in a murine pancreatic tumor model by administration of CD40 agonistic antibody and ICB (PD1 and CTLA-4 blockade) in combination with 20 Gy focal irradiation to one metastatic deposit [56].

With the advent of immunotherapy (IMT), there are increasing clinical reports of abscopal effects in humans. For example, indolent B cell non-Hodgkin lymphoma patients treated by TLR9 agonist combined with 2x2 Gy RT (the TLR9 agonist was injected at a single disease site once before the RT and 9 cycles afterwards) led to an overall response rate (ORR) of 27%, and abscopal effects in 2/15 patients [57]. As another example, abscopal responses were reported for melanoma and renal cell carcinoma patients treated with stereotactic body radiation therapy (SBRT) given in one, two or three doses of 20 Gy,

in combination with IL-2 [58]. In a recent clinical trial including heavily pre-treated patients having TIL negative or excluded tumors (ovarian, colorectal cancer, breast and cholangiocarcinoma), the delivery of 30-50 Gy in 3-5 fractions in combination with a PD-L1 inhibitor (administered within 7 days after completion of SBRT), the ORR in non-irradiated sites was 13%, and the investigators showed that local control was the same for both fully and partially irradiated tumors (tumors measuring more than 65 cm^3 that could not be fully covered with tumoricidal doses of SBRT) [59]. Other case reports of abscopal effects can be found in our recent publication [12].

Approaches for increasing abscopal responses to radio-immunotherapy

The main immune cell-type involved in direct tumor cell destruction following RT and IMT are cytotoxic T lymphocytes, but their effectiveness is dependent upon support received from other immune cells, such as antigen presentation and co-stimulation by activated DCs. Moreover, effector T cells can quickly be rendered anergic or exhausted by a plethora of suppressive mechanisms that can be upregulated in the TME. Thus, as we aim to improve patient outcome in the era of immune-oncology, it is evident that all aspects of the cancer immunity cycle, including, (I) the release of cancer antigen, (II) cancer antigen presentation by activated APCs, (III) priming and activation of T cells, (IV) trafficking and infiltration of T cells into the tumor and, (V) recognition and killing of cancer cells, as well as specific barriers that are present in a given tumor, must be taken into careful consideration in the design of combinatorial therapies that are personalized, synergistic and as minimally toxic as possible [60].

While RT itself can promote tumor antigen upregulation and presentation by tumor cells, as well as recruit DCs and T cells, the phenotype of the APCs may be such that they do not provide sufficient co-stimulation. In such situations, anti-CD40 antibody, or TLR agonists, can be employed to differentiate the DCs [56, 61, 62]. ICB of the PD1/PDL1 axis, and CLTA-4 could provide further synergy to the combination by releasing the brakes on T cells and enhancing their priming [60, 63]. It is conceivable that a combination of RT, anti-CD40 Ab or TLR agonist, plus ICB, be sufficient to overcome barriers to an abscopal effect in a patient. However, additional suppressive mechanisms may be at play in a given TME, such as Tregs, MDSCs or M2 macrophages, that themselves have the capability of blocking an abscopal effect [64]. Additional therapies, such as metronomic cyclophosphamide to deplete Tregs [65-67], or antibodies targeting TGFβ, may be used to overcome these barriers. Low-dose (non-tumoricidal) irradiation to metastatic deposits could also be beneficial in the event that they are cold or excluded [11, 68, 69]. Finally, cytokine administration, such as of IL-2 at the peak of tumor antigen release by RT, may help to maximize the effect of T cells that have infiltrated the tumor [58, 70].

Of course, the greater the number of treatment modalities combined, the greater the risk of toxicity. Notably, administration of ICB targeting PD1/PDL1 as well as CTLA-4 in concomitance with SBRT was shown to be safe in a recent study that included patients treated with different fractionation schemas to the lung (SBRT 50 Gy/4 fractions or 60 Gy/10 fractions, 45 Gy/15 fractions, and 45 Gy in twice-daily fractions) [71]. Both the tolerability and noninvasive character of RT make it the ideal partner for combinations with novel immunotherapeutic agents, such as adoptive transfer of chimeric antigen receptor or TCR-engineered T cells [72], treatment with ICB, tumor vaccines, or immunogenic chemotherapy. Clinical trials exploring different doses, volumes and fractionations of RT in combination with IMT are critical to advance the field of radio-oncology. Indeed, as depicted in **Figure** 1, low versus conventional versus high doses of irradiation will upregulate different immune supporting and suppressive mechanisms, which may subsequently lead to the need for different combinations of IMT for best patient responses. Such innovative trials should therefore include deep interrogation of blood and tumor biopsies in order to understand how radiation impacts the TME as well as the mutational load of a given tumor. Finally, other forms of RT, such as with protons, carbon ions and flash irradiation, should also be evaluated for their capacity to induce abscopal effects and tumor control in combination with IMT.

Concluding Remarks

The combination of RT and IMT is a game changer for radiation oncologists as the focus in this field shifts from direct tumor cell destruction to TME reprogramming and immune-modulation. While RT can be applied to promote many aspects of the tumor immunity cycle, including tumor antigen presentation, vasculature normalization, T cell and DC recruitment (*i.e.* turning cold tumors hot) and activation, a variety of suppressive mechanisms, including influx of Tregs and MDSCs, are also set into motion. The combination of immunomodulatory agents with RT that can act synergistically to further promote the activity of favorable immune cells (*i.e.* T cells and DCs), as well as block or reprogram inhibitory ones (*i.e.* MDSCs, M2 macrophages and Tregs), will improve abscopal responses in patients. Critical open questions in the field remain the identification of tumor biomarkers to select best combinations of immunomodulatory agents, as well as optimal radiation doses, volumes and fractionations. The kinetics of the cellular

and molecular events triggered in the TME by different RT modalities and sequences of treatments should provide valuable clues as to the optimal window of opportunity for RT to potentiate IMT interventions that may be tumor-type specific. These are the questions at the cutting edge of modern RT that call for innovative multidisciplinary translational research initiatives.

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Swiss Hyperthermia Clinical and Research Activities: Integrating with Radiation Therapy

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Hyperthermia (HT), a cancer therapeutic modality raises the loco-regional tumour temperature in the range of 39-45°C [1]. Temperatures above 45°C are considered as thermal ablation. The resurgence of HT for cancer therapy came subsequent to the several *in vitro* and *in vivo* studies reported during the latter half of the last century following systematic evidence of a thermal dependence of cell kill and its potentiation by radiotherapy (RT). This prompted clinicians to use HT either alone or in combination with RT and/or chemotherapy (CT) for various sites. Nonetheless, by the end of the last century, there was a subtle dampening in the enthusiasm for HT in clinical practice. This was due to lack of proper heating and temperature monitoring equipment and some equivocal reports on outcomes that could be attributed to unsatisfactory heating techniques.

HT alone or in combination with RT and CT is well tolerated, safe and reported to be without any significant acute or late toxicity [1]. It's one of the most potent radiosensitizers and is also synergistic to a number of chemotherapeutic agents (**Fig.** 1). It is indeed a unique therapeutic modality with multifaceted actions, having favorable interaction with RT and/or CT and is also a potential immunomodulating agent, akin to "*in situ* tumour vaccination" [2]. Furthermore nanoparticle based HT, an emerging field of research, is capable of heating tumour "inside out". In view of the closer proximity to the tumour vasculature, the nanoparticle based HT results in higher global parenchymal tumour temperatures. It also has been shown to specifically sensitize the tumour stem cells. When decorated with critical payloads of radionuclides, nanochemotherapeutic agents, immunoconjugators, gene silencing macromolecules with siRNA and miRNA; these nanoparticles have the enhanced potential of delivering precisely multimodality therapy analogous to "nano" bullet [3]. HT therefore deserves a closer attention for getting integrated in the routine therapeutic armamentarium along with surgery, RT, CT and immunotherapy.

Hyperthermia activities in Switzerland

A. Hyperthermia facilities with radiotherapy

Presently, the Kantonsspital Aarau (KSA) has both superficial and deep HT treatment facilities. The superficial HT system was installed in 2006 while the deep HT unit has been in operation since 2010. The department has been treating patients referred for HT along with RT and/or CT, namely recurrent breast cancers, head and neck cancers, muscle invasive bladder cancers (MIBC), cervix cancer, soft tissue sarcomas, chordomas, malignant melanoma, locally advanced pancreatic cancers (LAPC), ano-rectal cancers and others [4-6]. In addition, Lindenhofspital Bern has facilities for superficial HT mainly for locally recurrent breast cancers [7], while superficial treatment facilities have been recently started at the University Hospital Geneva (HUG). For deep seated HT, HUG is exploring the feasibility of using MR guided high intensity focused ultrasound.

B. Approval of hyperthermia by The Federal Office of Public Health (BAG), Switzerland

In December 2016, BAG based on the present evidence of HT for superficial and deep seated tumours had approved reimbursement in compulsory outpatient health care insurance catalogue to four indications for superficial HT without any restrictions (recurrent breast cancers, inoperable lymph node metastasis in head neck cancers, malignant melanoma and local residual tumour with compression symptoms). For deep HT, BAG has approved

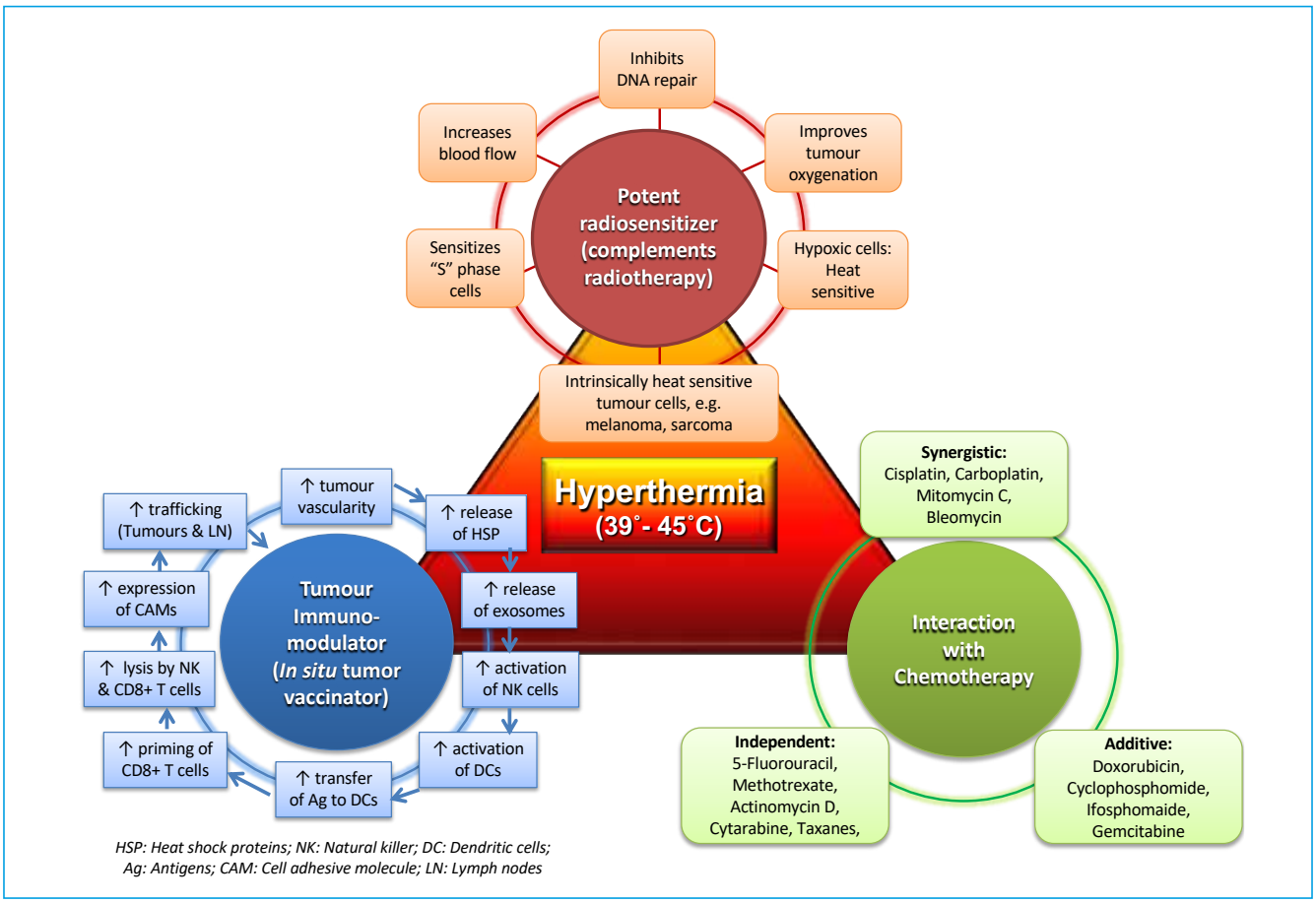

Fig. 1. Multi-faceted action of local hyperthermia at 39-45°C.

five indications in patients with cancer cervix, LAPC, soft tissue sarcoma, MIBC and rectal cancer for a 2-year period with reassessment by December 2018.

C. Swiss Hyperthermia Clinical Network

As per the BAG directives, it is mandatory that all Swiss patients be presented and discussed at the weekly Swiss HT Tumor Board with participating institutions joining on WebEx. A Swiss HT Network was therefore established in 2017 to discuss all patients that could be potentially considered for HT. Till March 2018, 46 HT tumour board meetings have been conducted in which 132 patients were presented and discussed. 113 of them were approved for HT treatments (superficial HT, n=81; deep HT, n=51). The tumour board is held with all participating centres once every week. Presently 12 Swiss centres are part of this clinical network. Joining this network is open to all Swiss centres (**Fig.** 2).

D. Swiss Hyperthermia Research Network

To promote scientific research, clinical studies and technical developments in the field of HT, the Department of Radio-Onkologie, KSA-KSB, Kantonsspital Aarau has taken a leadership role in integrating various research institutions in Switzerland under the umbrella of Swiss Hyperthermia Research Network to promote clinical, technical, basic and translational research in HT (**Fig.** 2). This was instituted on October 19, 2012, and has active participation from several institutions of Switzerland, USA and Europe. The various activities undertaken are:

1. *Clinical trials:* Three ongoing clinical studies approved by the Swiss Ethical Commissions are open for patient recruitment from all Swiss centres. These studies are:
   i. A phase IIB study of the tetramodal therapy of T2-T4 Nx M0 bladder cancer with HT combined with chemoradiotherapy (CTRT) following transurethral resection of bladder tumour (TUR-BT). This study is intended to explore the safety and efficacy of combined RT, CT and HT in elderly patients of MIBC who are unfit for any major surgical interventions [6].
   ii. A phase II randomized study of concurrent HT and CTRT vs. CTRT alone following neoad-

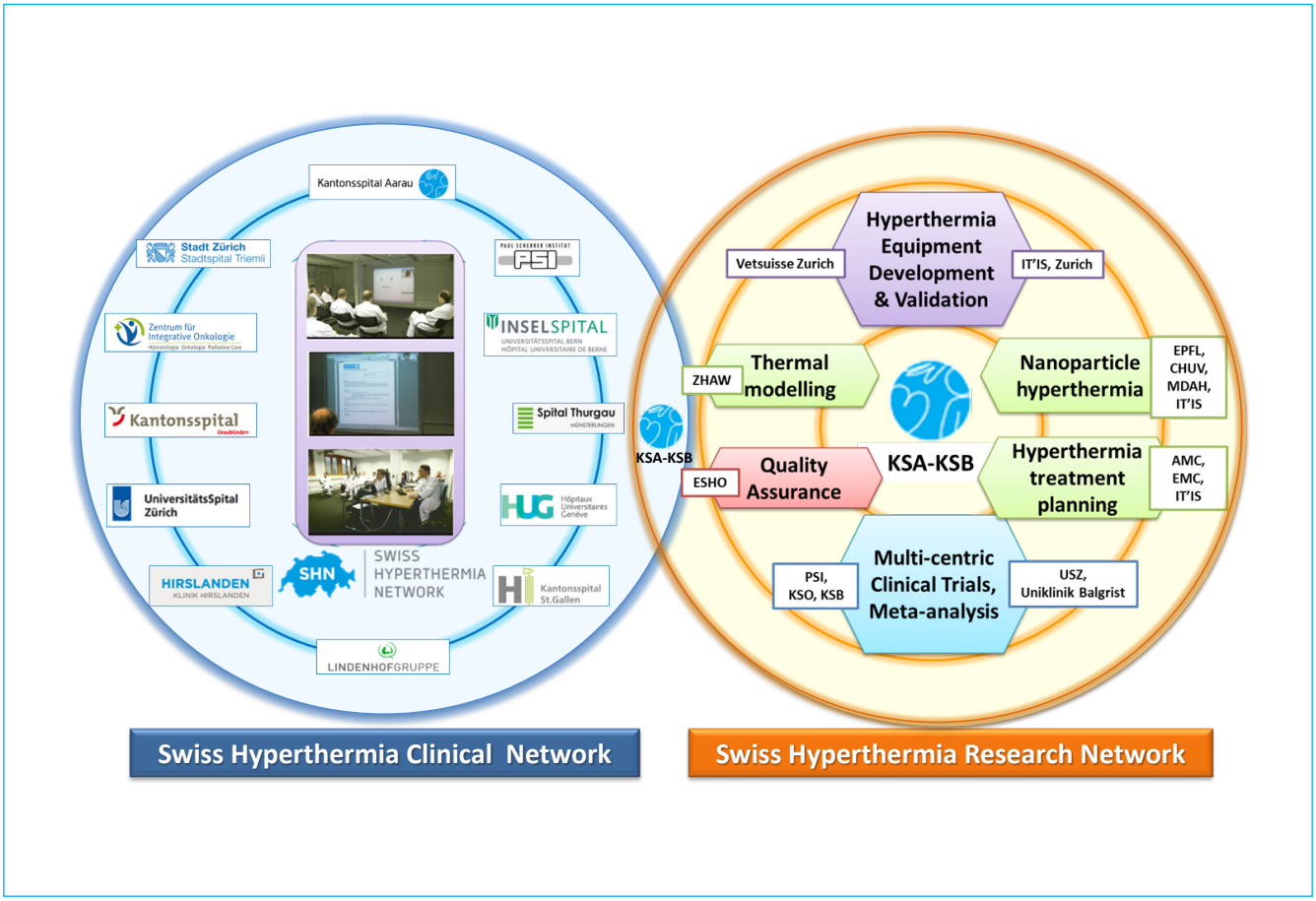

Fig. 2. Swiss Hyperthermia Clinical Network partners and Swiss Hyperthermia Research Network collaborators and ongoing research projects. Institution/s involved in each of the research projects are indicated in abbreviation/s.

juvant CT in LAPC (HEATPAC) (*ClinicalTrials.gov* NCT01904565) [4]. Since most of patients of LAPC have very poor outcomes, the proposed study is designed to explore the efficacy of local HT along with the conventional CTRT as a phase II randomized trial. This is based on the strong thermoradiobiological basis and with the potentiation of RT and CT (especially gemcitabine), the outcomes are expected to be in favour of HT with CTRT. Further, gemcitabine is also a radiosensitizer and thus, the combination promises to provide an improved therapeutic ratio without any added toxicity.

iii. A phase I/II study of concurrent HT and proton beam RT in primary and unresectable soft tissue sarcoma (HYPROSAR) (*ClinicalTrials.gov* NCT02439593)[2, 8]. This phase I/II study uses proton beam RT and local HT for primary unresectable and recurrent soft tissue sarcoma. This is a novel approach and is based on taking the physical dose distribution advantage of protons and thermoradiobiological advantanges of HT.

2. *Collaboration with IT'IS to develop a superficial HT treatment unit:* The unit has been successfully tested in animal tumours at the Vetsuisse Zurich and has been found to be effective to deliver HT in superficial tumours [9]. Efforts are ongoing to process for CE certifications so that this could be also used in humans.

3. *Collaboration with IT'IS from development of a deep HT unit:* The project has been initiated with support from University of Zurich and currently this is under "work in progress".

4. *Quality assurance guidelines:* The department of Radiation Oncology Center KSA-KSB, Kantonsspital Aarau has been involved in formulating European Society Hyperthermic Oncology (ESHO) guidelines for superficial HT. These are now inforce at all HT centres in Europe [10, 11]. The next phase is to develop similar guidelines for deep seated tumours. KSA is involved in this effort and is being carried out in joint collaboration with other participating centres of Europe under the auspices of ESHO.

5. *Development of a phantom for quality assurance (QA) checks of HT units:* KSA has designed and developed inhouse a unique HT phantom that would be used for conducting various QA checks for HT treatment systems. The phantom is unique and in contrast to the commerically available multi-lighted bulb phantom, uses a single diode detector to scan the signals in all 3 axes. The equipment can also be used to measure directly the SAR values with a SAR probe. Presently, the system is undergoing field testing at KSA.
6. *Modelling:* ZWAH, one of the collaborators is primarily looking to develop various thermoradiobiological models that could be used to design treatment strategies with HT and RT [12].
7. *Integrated hyperthermia and radiotherapy treatment planning:* Development of this integrated thermoradiotherapy treatment planning system is being undertaken along with our other European collaborators (AMC, EMC) and IT'IS.
8. *Conduct of meta-analysis:* Since meta-analysis is considered to provide level I evidence in clinical practice and decision making, three meta-analysis/network meta-analysis have been conducted. These include in recurrent breast cancers, locally advanced head and neck cancers and locally advanced cancer cervix. In head and neck cancers, HT along with RT enhances the likelihood of CR rates by around 25% compared to RT alone with no significant additional acute and late morbidities [13]. In locally advanced cancer cervix, the complete response and long term control improved by 22% and 23% respectively over RT alone without significant increase in morbidity [14]. In loco-regional recurrent breast cancers, results from 34 studies, totaling to 2110 patients, show that RT and HT could provide a complete response in more than 60% of these patients [15]. Even those who were re-irradiated, 66.6% achieved a complete response without any additional significant treatment morbidity.

Thus, the HT clinical and research activities in Switzerland are closely intertwined to scientifically evaluate the utility of HT along with RT and/or CT in various tumour sites. It has been a constant endeavor on the part of all the collaborators of this HT network to address the challenges posed by the multifaceted action of this unique modality in a scientific way. This could help boost the confidence amongst clinicians and pave the way for effective integration of HT along with other treatment modalities in the clinical oncology practice.

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AGORA, bien plus qu'un bâtiment, un pôle d'excellence pour la science et les patients

AGORA, la place où l'on se rencontre, quel nom pouvait-t-on trouver pour le bâtiment dédié à la recherche sur le cancer qui s'ouvre cette année à Lausanne? Assurément aucun autre. Depuis plus de deux millénaires, il symbolise le dialogue, le partage, la réflexion qui mènent à l'action.

Le cancer, problème majeur de santé publique interpelle. Il suscite émotions, craintes et beaucoup d'interrogations. La Fondation ISREC, active depuis 1964 dans la recherche dans le domaine de l'oncologie, a décidé d'investir une partie importante de ses ressources pour bâtir un lieu emblématique dans le but de créer un pôle de recherche fort et reconnu consacré au cancer. Il réunira les meilleurs spécialistes provenant de disciplines à la fois variées et complémentaires pour travailler, ensemble, au service des patients. La Fondation ISREC a toujours été attentive et le sera à l'avenir, pour que du laboratoire au lit du malade *(bench to bed),* le patient et ses proches ne soient pas oubliés, mais partenaires du défi de mieux comprendre cette maladie et de trouver des traitements adéquats pour y faire face. Construit en face du bâtiment des soins du CHUV, AGORA donnera aux chercheurs cliniciens l'opportunité d'être à deux pas tant de leurs patients que de leurs laboratoires, évitant ainsi des temps de transports inutiles, une manière de les encourager à se consacrer aux deux activités.

Certes, les enjeux sont majeurs, mais les espoirs aussi. La réunion des institutions de l'arc lémanique pour œuvrer en commun aux missions de recherche dans le domaine oncologique constitue aussi un événement à saluer, démontrant que pour les défis d'importance, les frontières sont dépassées. Il faut s'en réjouir. La Fondation ISREC a toujours œuvré dans ce sens, elle continuera à le faire. AGORA représente cette volonté commune de s'engager au service d'une cause qui ne laisse personne indifférent et qui mérite les meilleurs spécialistes pour répondre aux attentes qu'elle suscite.

Catherine Labouchère
Présidente de la Fondation ISREC, Lausanne

De gauche à droite: Prof. Franco Cavalli, président du Conseil Scientifique de la Fondation ISREC (président IOR, Istituto Oncologico di Ricerca), Mme Catherine Labouchère, présidente du Conseil de la Fondation ISREC (juriste et députée au Grand Conseil vaudois), Prof. Dr. Michael N. Hall, membre du Conseil Scientifique (professeur au Biozentrum de l'Université de Bâle), Prof. Dr. Anne Müller, membre du Conseil Scientifique (professeure associée en médecine expérimentale à l'Institut de recherche moléculaire sur le cancer à l'Université de Zurich), Prof. Francis-Luc Perret, directeur de la Fondation ISREC, Prof. Fabrice André, membre du Conseil Scientifique (directeur de recherche, responsable de l'unité U981 INSERM et professeur associé au département d'oncologie médicale à l'Institut Gustave Roussy, Villejuif, France). Absent: Prof. Peter Johnson, membre du Conseil Scientifique (professeur en oncologie médicale à la faculté de médecine de l'Université de Southampton, UK).

AGORA, the flagship of the Swiss Cancer Center - Léman

Prof. Dr. George Coukos, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne (UNIL) and Ludwig Institute for Cancer Research (LICR)
Prof. Pierre-Yves Dietrich, Hôpitaux Universitaires de Genève (HUG)
Prof. Doug Hanahan, École Polytechnique Fédérale de Lausanne (EPFL)

* The pictures contained in this article represent the AGORA building viewed from different angles.

Introduction

This is a landmark year for oncology in the Lemanic region, with the official launch of the new Swiss Cancer Center - Léman (SCCL) and the opening of its flagship building, AGORA. SCCL aims to establish a highly integrated, multidisciplinary and collaborative cancer research and clinical community focused at fundamental and translational cancer research investigating and solving urgent cancer problems through the development of new therapeutic strategies in concert with rapid and effective translation to the clinic. UNIL, CHUV, UNIGE, HUG and EPFL signed in 2016 a memorandum of understanding to develop such a partnership. The SCCL further includes the participation of privileged partners, i.e. the ISREC Foundation and the Ludwig Institute for Cancer Research (LICR). Finally, the SCCL will include the Réseau romand d'oncologie, a clinical oncology network established in the French-speaking Switzerland to encompass all medical oncology practitioners in the community and the two university hospitals. The SCCL is led by an Executive Committee composed by Professors George Coukos, Douglas Hanahan and Pierre-Yves Dietrich.

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Today, the five-institution consortium features at least 80 cancer research groups, whose activities span basic, translational and clinical research, while the innovative new clinical network of oncology includes over 100 oncologists with the intent to collaborate in guiding optimal therapeutic decisions for cancer patients, coordinating clinical trials and implementing «precision oncology» for the regional population of approximately 2 million people.

Driving integrated cancer research and collaborative efforts within this uniquely diverse and complementary community is a key priority of the SCCL to create synergies, unparalleled opportunities for discovery, and pave the way for the development of innovative science and its translation to the clinic.

The SCCL is therefore set to achieve the following specific goals: I) Therapeutic innovation, i.e. developing new anticancer technologies in particular in the areas of tumor immunology, immune engineering and immunotherapy, precision radiotherapy and nuclear medicine, together with testing new mechanism-guided cancer therapies through clinical trials; II) Cancer detection and prevention, i.e. understanding and reducing environmental, behavioral or genetic risk factors, boosting immunity, and developing new technological methods for early tumor detection; III) Multidisciplinary research that fosters synergy and integration across basic, translational and clinical cancer research frontiers, and IV) Inspirational training that supports the career development of the next generation of cancer research scientists, cancer bioengineers and cancer clinicians.

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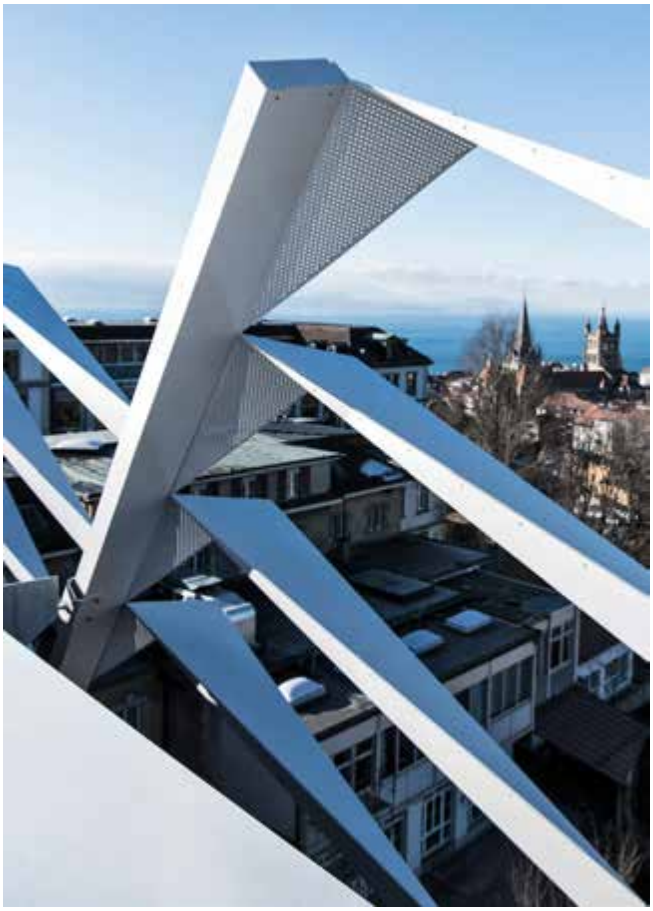
The AGORA building

Slated to be launched in November 2018 after the inauguration day on October 3rd 2018, the AGORA translational cancer research building will be the flagship of the research and therapeutic development activities of the SCCL. Built thanks to an 80 million CHF financial investment by the ISREC Foundation and designed by the German architect Stefan Behnisch, the rather spectacular and visionary four-story building harbors a flared structure from the floor to the roof with no right angle, and fits harmoniously the space between the Pathology Department building of the CHUV on one side, with which it is joined by a glass-roofed large atrium, and a natural urban forest on the other side, above which spectacular views of the city and the lake can be captured.

Inside, the building offers 5000 m^2 of equipped research laboratory space and 2900 m^2 of advanced facilities, all dedicated to translational and interdisciplinary research. By stimulating the transfer of a scientific discovery made in the laboratory to concrete clinical applications and rapid benefit to the patient, translational research will bring innovative therapeutic approaches to the bedside. With its strategic location on the hospital campus, and direct connectivity with the Institute of Pathology through an atrium, AGORA is positioned to accelerate the development and delivery of state-of-the-art therapies to the patients both nearby and afar.

The AGORA building will welcome around 250 transdisciplinary researchers including fundamental cancer biologists, cancer immunologists, clinician-scientists, bioengineers and bioinformaticians from different departments of UNIL and CHUV as well as the LICR, from two EPFL Institutes, the Swiss Institute for Experimental Cancer Research (ISREC@EPFL) and the Institute of Bioengineering (IBI), and groups from UNIGE and HUG. This clustering of inter-disciplinary, multi-institutional cancer research competences under one roof is visionary, making AGORA an incubator for innovation. The teams will be distributed over three floors of laboratories programmed into thematic «research areas». This thematic organization will also accelerate the development of new, more effective and targeted therapies for patients.



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AGORA was designed to promote interactions. The «open» interior architecture of AGORA will enable and foster formative collegial interactions in artfully designed «bumping spaces» where researchers meet by plan or by chance, as they sit at the café for example, or transition through the building. An expansive atrium will also encourage communication via planned or accidental encounters. In addition, the open/contiguous research laboratory spaces were designed to ensure seamless integration between research teams of complementary expertise, allowing informal meetings to take place. Importantly, vertical interactions between floors – inconvenient in traditional building designs – will be facilitated by invitingly open staircases that connect the three research floors. Offices are clustered to enhance interactions among leading investigators, and generous space is dedicated to clinicians and bioinformaticians. Importantly, an additional key component of AGORA is that it will provide «hotel lab space» throughout the building. This protected space will be purposely located between larger permanent labs, in such a way that the temporary occupants of this lab space will be fully integrated scientifically and will have access to shared equipment on the floor. For example, this space will be useful to host junior faculty transitioning to independence, who can benefit from close interactions with and mentorship from the established PIs present in the AGORA. In summary, AGORA will offer a rare proximity between leading complementary labs and afford exceptional opportunities to the scientists to reshape their research and launch innovative intra- and cross-disciplinary collaborations on specific themes.

• ***The scientific programs and technology platforms***

The scientific research programs at AGORA will focus on the molecular mechanisms of tumor biology, in particular the immunology of tumors, and will leverage the exploration of the immune system as a powerful therapeutic weapon against cancer. The mission at AGORA is therefore to create both a scientific and a clinical impact. The success of these programs will rely on the seamless integration between basic and translational research, the development of new technologies and therapeutic concepts, and clinical analyses.

The research programs in the AGORA, supported by cutting-edge technology platforms, will focus on the following disciplines:

• ***Tumor Microenvironment and Therapeutic Development***

This program will seek to investigate the complex interactions of tumor stroma and host immune cells with tumor cells, and understand how healthy host cells are recruited, corrupted and induced to support tumor progression and resistance to current therapies. The knowledge acquired will trigger translation into therapeutic strategies targeting mechanisms at the tumor microenvironment using preclinical models. New knowledge-based rational combinatorial therapeutic approaches will be investigated in a variety of solid tumor systems, with the aim of developing new clinical solutions for patients. The close collaboration of cancer biologists, immunologists, bioengineers, molecular imaging experts, clinician-scientists, bioinformaticians and systems computational biologists will be key to accelerate discovery and clinical translation.

• ***Human Tumor Immunology Discovery and Bioengineering***

In an integrated research approach, this program will bring together researchers from the Lausanne branch of the Ludwig Institute at UNIL and CHUV specializing in cancer immunology, bioengineers from EPFL, and bioinformaticians, who will focus on human tumor immunology and T cell dysfunction with the ultimate goal of developing new T cell therapies.

The program will integrate the following three themes:

– *Systems human cancer immune biology:* when cancer biology and immunology meet biocomputation

Biologists and bioinformaticians will work together to provide a thorough and systematic answer to the questions raised about the function and interdependence of tumor cells, their microenvironment and the immune response focused on human tumors. This research will encompass in-depth high dimensional interrogation of human tumors, their microenvironment and the immune response, the understanding and circumventing of mechanisms of tumor immune suppression, the development of approaches to reactivate antitumor immunity, and the elucidation of the interdependencies between cancer cell-intrinsic and tumor microenvironment mechanisms.

– *Technology development:* when cancer biology and immunology meet bioengineering
Immunoengineering will be a key area of research. Biologists and bioengineers will collaborate to develop breakthrough bioengineering tools and apply these new technologies to tumor immunobiology, in particular T-cell dysfunction in the tumor environment, aimed to correct and enhance their anti-cancer performance. This will especially include the development of new *in vitro* tumor surrogate models for drug testing, the development of technology for deeper and accelerated interrogation of human tumors and their microenvironment, as well as the development of culture devices to support personalized T-cell therapy.

– *Immunotherapy:* when cancer biology and immunology meet the clinic
The clinical impact will be explored here between scientists and clinicians with the identification of opportunities such as the discovery of immunogenic tumor antigens applicable to the development of adoptive cell transfer therapy with T lymphocytes.

• ***Metastasis and Molecular Imaging***
This program will notably be dedicated to the discovery and application of novel radiotherapy and nuclear medicine technologies to molecular imaging and therapeutic targeting of tumors, particularly metastases. Interdisciplinary teams will therefore seek to identify new, more precise methods of diagnosis, monitoring and targeted treatment of metastases. Remarkably, targeted radio-nuclear therapy will be combined with molecular nuclear-based imaging (molecular nuclear theranostics) to offer new therapeutic solutions to cancer patients. This program will benefit from the expertise of research groups investigating the biology of different cancer types in AGORA and in SCCL. Cancer computational biology will be incorporated to provide bioinformatics support for data analysis, mining and algorithmic development.

• ***Precision and «big-data» Oncology***
This program aims to integrate the personalization of oncology treatments in the care of patients of the CHUV and the entire network in Western Switzerland (Suisse Romande). In order to predict the best strategic options for a given patient, this «big-data» clinical division will therefore develop cutting-edge machine-learning algorithms and bioinformatics infrastructures to collect, integrate, analyze and interpret high-dimensional data including clinico-pathological information, molecular data (genetics, genomics, proteomics, etc.), laboratory results on mechanisms and vulnerabilities (sensitivity to drugs, etc.). Multidimensional predictive biomarkers for immune therapies will be one of the prime focus of this program. The unit will consist of oncologists, bioinformaticians and software engineers as well as data processing specialists.

• ***The technology platforms***
To support and ensure a successful running of the scientific programs, AGORA will host cutting-edge technological facilities. These include:

– Platforms dedicated to new technologies being developed by bioengineering laboratories from EPFL and to their collaborative projects with the cancer biologists and immunologists.

– A Mass Spectrometry platform for tumor antigen detection in personalized cancer immunotherapy.

– A Flow Cytometry Facility for cell sorting and both classical and imaging flow cytometry analysis.

– An *in vivo* Imaging Platform for high resolution *in vivo* preclinical research including MRI, micro-CT scanning, two-photon microscopy, stereotactic radiation etc.

– Cellular Imaging Facility, which will assist the researchers with additional imaging needs spanning wide-field fluorescence and transmission optical microscopy, confocal microscopy, two-photon microscopy, light sheet microscopy, time-lapse and ion imaging, *in vivo* bioluminescence and fluorescence measurement in anesthetized animal, laser capture microscopy, and digital image processing and analysis.

– An AGORA *In Vivo* Center, a state-of-the-art facility for preclinical work and trials involving instrumental cancer models. This facility, designed to meet the required veterinary regulatory standards for its operation, will actually house the above-mentioned *in vivo* Imaging Platform and be equipped with modern rack washers, autoclaves, surgical suites, and general procedure areas.

– A Mouse Pathology Facility providing expertise and equipment for histology, performing routine tasks like tissue sectioning and classical staining, as well as establishing and optimizing project-specific histological methods, developing and delivering protocols.

AGORA, at the center of a global network

In addition to fostering scientific exchanges and interdisciplinary collaborations between its scientist residents, AGORA aims to explore complementary strengths and opportunities in building research partnerships with external institutional departments from the Lausanne area as well as from other Swiss Institutes. On one hand, AGORA aspires to create a powerful interdisciplinary, interdepartmental and inter-institutional cancer research hub focused in significant parts on the breakthrough frontiers of cancer immunology and immunotherapy. On the other hand, AGORA also aims to catalyze important interactions across broad domains of medicine so as to accelerate discoveries that can be complementary and synergistic to traditional therapeutic modalities. In the same vein, AGORA will reinforce its interactions with the pharma industries as key partners for translational cancer research and drug and therapy development.

In conclusion, the AGORA – as the flagship of the SCCL and a focal point of its operations – will enable exciting developments and advances in translational and clinical cancer research in order to deliver the latest innovative therapies to cancer patients. Seeking to promote scientific excellence worldwide, the SCCL at large and the AGORA in particular will unite cancer scientists into an integrated «comprehensive» cancer research enterprise in Switzerland.

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HOVON 127 BL / SAKK 37/16 Optimierung der Chemotherapie beim Burkitt-Lymphom

Die Haemato Oncology Foundation for Adults in the Netherlands (HOVON) und die Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) vergleichen in dieser Phase III Studie zwei Chemotherapieschemata beim neu diagnostizierten Burkitt-Lymphom.

Das Burkitt-Lymphom ist ein B-Zell-Lymphom und macht bei Erwachsenen etwa 1-5% aller Non-Hodgkin-Lymphome aus. Das Burkitt-Lymphom gilt als Hochrisiko-Tumor und der allgemeine Konsens bezüglich der Behandlung beinhaltet eine rasche, aggressive Chemotherapie und/oder Strahlentherapie. Allerdings sind weltweit keine grossen randomisierten Studien durchgeführt worden, die ein optimales Behandlungsschema für Erwachsene aufzeigen. Ziel der Studie Hovon 127 BL / SAKK 37/16 ist eine Verbesserung des Behandlungsergebnisses und der Verträglichkeit der Chemotherapie beim Burkitt-Lymphom.

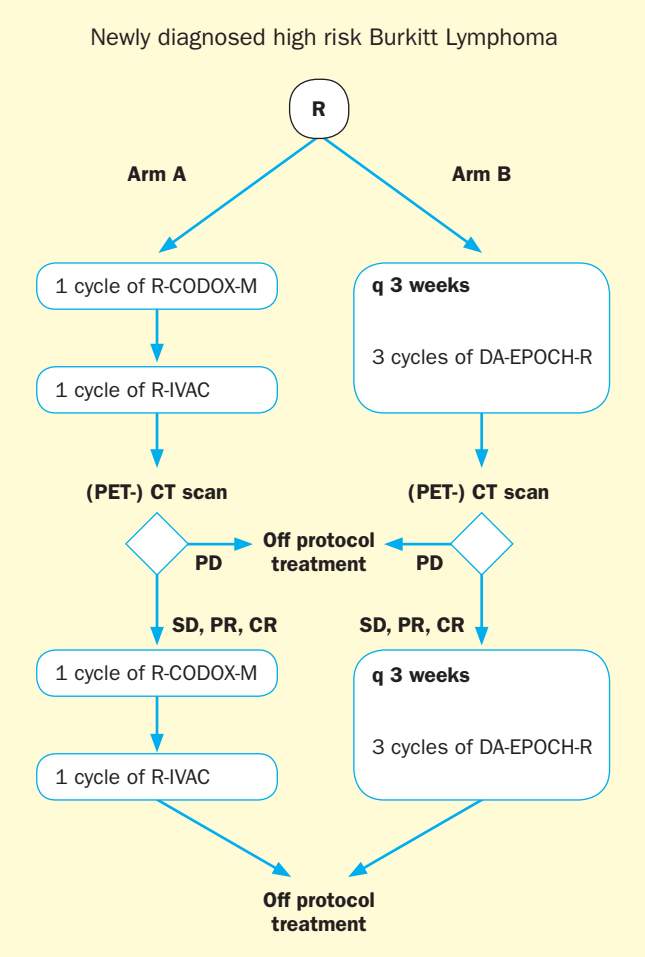

Abb. 1. Studiendesign HOVON 127/ SAKK 37/16.

Die randomisierte Studie vergleicht das Chemotherapieschema DA-EPOCH-R[1] mit dem Standardschema R-CODOX-M/R-IVAC[2]. Beides sind international anerkannte Therapien beim Burkitt-Lymphom, jedoch zeigte in einer früheren Phase II[3] Studie das Schema DA-EPOCH-R eine erhöhte Wirksamkeit und verringerte Sterberate (keine Grössenzunahme des Tumors und/oder neue Metastasen bei 85% der Patienten nach 2 Jahren bzw. progressionsfreies Überleben von ca. 70% nach 2 Jahren) gegenüber der Behandlung mit R-CODOX-M/R-IVAC. In der aktuellen internationalen Studie soll dieses Resultat nun in einem grösseren Rahmen (260 Patientinnen und Patienten) bestätigt werden.

Die Gesamtstudiendauer für die einzelnen Patienten beträgt 16–18 Wochen, gefolgt von Nachsorgeuntersuchungen über die nächsten fünf Jahre. Alle in dieser Studie verwendeten Medikamente sind in Europa und der Schweiz zugelassen.

Studiendesign: Prospective, multi-center, randomized phase III study, siehe **Abb. 1**.

Studienname: Phase III study comparing R-CODOX-M/R-IVAC versus dose-adjusted EPOCH-R (DA-EPOCH-R) for patients with newly diagnosed high risk Burkitt lymphoma

Teilnehmende Zentren:
Universitätsspital Basel, IOSI Bellinzona, Inselspital Bern, Kantonsspital Luzern, Universitätsspital Zürich

Prof. Dr. Frank Stenner

Coordinating Investigator:
Prof. Dr. Frank Stenner, frank.stenner@usb.ch, Universitätsspital Basel

Clinical Project Manager:
Michelle Schaffer, michelle.schaffer@sakk.ch, SAKK Bern

1. Dose Adjusted – Etoposide, Prednisone, Oncovin (vincristine), Cyclofosfamide, Hydroxydaunorubicine (doxorubicine) und Rituximab.
2. Rituximab, Cyclofosfamide, Oncovin (vincristine), DOXorubicin, Methotrexate/Rituximab, Ifosfamide, VP-16 (etoposide), ARA-C (cytarabine).
3. Dunleavy K, et al. Risk-Adapted Therapy in Adults with Burkitt Lymphoma: Preliminary Report of a Multicenter Prospective Phase II Study of DA-EPOCH-R . Blood (ASH 2015) 126: 324. 2015.

SAKK 10/16 – Vergleich der «Best of»-Strahlentherapie und «Best of»-Operation beim frühen oropharyngealen Plattenepithelkarzinom

Die European Organisation for Research and Treatment of Cancer (EORTC) und die Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) vergleichen in dieser Phase III Studie die primäre Strahlentherapie und die transorale Operation beim oropharyngealen Plattenepithelkarzinom im Frühstadium in Bezug auf das Wiedererlangen bzw. Beibehalten der Schluckfunktion.

Das oropharyngeale Plattenepithelkarzinom entsteht im weichen Teil des Gaumens, den Mandeln oder dem Zungengrund und nimmt aufgrund der HPV-Assoziation und den Langzeitfolgen von Nikotin- und Alkoholmissbrauch zu. Als Standardtherapie haben sich sowohl der chirurgische Eingriff wie auch die Strahlentherapie etabliert. Der chirurgische Eingriff umfasst eine vollständige Entfernung des Tumors in der Mundhöhle und eventuell betroffener Lymphknoten im Hals. Die Möglichkeiten der plastischen Rekonstruktionen und zuverlässiger Defektdeckungen haben in den letzten Jahren zu einer Reduktion der Folgeerscheinungen und guten Lebensqualität der Patienten geführt. Die intensitätsmodulierte Strahlentherapie ermöglicht es, eine hohe Bestrahlungsdosis im Tumorzentrum zu platzieren, während das umgebende Gewebe deutlich besser als mit früheren Methoden geschont wird und damit eine gute Lebensqualität sichert. Mit beiden Verfahren werden bei den frühen Stadien hohe Heilungsraten erzielt.

Die Wahl zwischen den beiden Optionen basiert generell auf den individuellen Erfahrungswerten der Zentren. Ein direkter Vergleich der Behandlungen hat bislang nicht stattgefunden. Da sowohl die Operation als auch die Strahlentherapie ein sehr gutes Verhältnis von Verträglichkeit und Wirksamkeit aufweist, soll diese randomisierte Studie evaluieren, welche der beiden Therapievarianten mehr Vorteile für Patienten bietet hinsichtlich der Wiedererlangung bzw. des Erhalts einer guten Schluckfunktion und einer Verbesserung der allgemeinen Lebensqualität.

Im Rahmen der Studie SAKK 10/16 sollen innerhalb von 2 Jahren 170 Patienten behandelt und untersucht werden.
Studiendesign: Open-label, investigator initiated, multicenter, randomized phase III study

Studienname: Phase III study assessing The «best of» radiotherapy compared to the «best of» surgery (trans-oral surgery (TOS) in patients with T1-T2, N0 oropharyngeal carcinoma.

Teilnehmende Zentren: Kantonsspital Aarau, Universitätsspital Basel, Inselspital Bern, CHUV Lausanne, Kantonsspital Luzern, Kantonsspital St. Gallen, Universitätsspital Zürich

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Kommentar zur Studie von Coordinating Investigator Prof. Dr. Frank Zimmermann:

Prof. Dr.
Frank Zimmermann

In der Behandlung des frühen Oropharynxkarzinoms stehen sich mit dem chirurgischen Vorgehen einer enoralen Tumorresektion und möglicher plastischer Rekonstruktion sowie der modernen dynamischen intensitätsmodulierten perkutanen Strahlentherapie zwei moderne, effektive therapeutische Verfahren gegenüber. Beide können in frühen Stadien eine hohe Heilungsrate erzielen, sodass bei der therapeutischen Entscheidung auch der Erhalt der Lebensqualität mit dauerhaft guter Schluckfunktion relevant ist. Bei bis zu 10% der Patienten kann im Rahmen der Operation ein zervikaler lymphonodulärer Befall diagnostiziert oder im längeren Verlauf in beiden Therapiearmen ein lokales Rezidiv auftreten. Die dann notwendigen und möglichen Zweitbehandlungen mit ihren langfristigen Einflüssen auf die Lebensqualität sind in die Überlegungen bei der Studienplanung eingegangen.

Ziel der vorliegenden Studie ist es, erstmals einen fundierten Vergleich im Hinblick auf den Erhalt der Lebensqualität, die lokale Tumorkontrolle und das Gesamtüberleben zwischen zwei gleichermassen effektiven Behandlungen mit aber unterschiedlichem Nebenwirkungsspektrum zu erzielen.

Aufgrund der zunehmenden Rate an HPV-Infektionen, die mit dem oropharyngealen Karzinom vergesellschaftet sind, und der steigenden Inzidenz der Oropharynxkarzinome im jüngeren Patientenalter, kommt dem langfristigen Erhalt der Lebensqualität und einer guten Schluckfunktion eine besondere Bedeutung zu.

Es ist daher sehr zu begrüssen, dass sich zahlreiche europäische Zentren zur gemeinsamen Studiendurchführung entschieden und Sponsoren für die Klärung der wichtigen Fragestellung gefunden haben. Wichtig ist es nun, die geeigneten Patienten, die im Rahmen der Studie in sehr erfahrenen und qualitativ kontrollierten onkologischen Zentren angebunden werden, zur Teilnahme zu gewinnen und sie vom Nutzen für sie selber und für zukünftige Patienten zu überzeugen.

Dr. med. et Dr. phil. Matyas Ecsedi gewinnt das SAKK/ Dr. Paul Janssen Fellowship 2018

Das diesjährige SAKK/Dr. Paul Janssen Fellowship geht an Dr. Matyas Ecsedi vom Universitätsspital Basel. Die Preisverleihung fand im Rahmen der Juni-Halbjahresversammlung der SAKK im Technopark Zürich statt.

Die SAKK und Janssen-Cilag AG vergeben jährlich das mit CHF 30‘000.- dotierte SAKK/Dr. Paul Janssen Fellowship. Das Ausbildungsstipendium soll jungen Ärztinnen und Ärzten die Möglichkeit bieten, bis zu vier Monate an einer renommierten Forschungseinrichtung im Ausland zu verbringen, wo sie ihre Kenntnisse über klinische Krebsforschung verbessern und sich die nötigen Werkzeuge aneignen, um erfolgreich Studien durchführen zu können.

Mit dem SAKK/Janssen Fellowship wird Dr. Matyas Ecsedi am Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, USA eine klinische Weiterbildung auf dem Gebiet der zellulären Immuntherapie mit genmanipulierten T-Zellen absolvieren. Die Auszeichnung wurde ihm von Prof. Dr. med. Viviane Hess, Vizepräsidentin SAKK, und Dr. med. Holger Bartz, Director Medical Affairs & Compliance bei Janssen Alpine, an der Halbjahresversammlung der SAKK am 27. Juni feierlich übergeben.

Von links: Dr. med. Holger Bartz, Dr. med. et Dr. phil. Matyas Ecsedi, Prof. Dr. med. Viviane Hess

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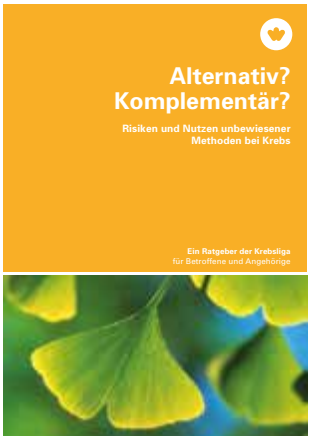

Expertengremium für Krebsfrüherkennung

Welche Massnahmen für die Krebsfrüherkennung sinnvoll sind, wird in der Öffentlichkeit und in der Fachwelt regelmässig kontrovers diskutiert. Deshalb benötigen die Entscheidungsträger im Gesundheitswesen qualitativ gute, unabhängig erarbeitete und ausgewogene Empfehlungen für diesen Bereich. Im Rahmen der Nationalen Strategie gegen Krebs (NSK 2014–2020) wird nun ein Expertengremium aufgebaut, das sich mit Fragestellungen zu bevölkerungsbezogener Krebsfrüherkennung (population-based screening) befassen und Empfehlungen erarbeiten soll. Ziel ist es, dass die Behörden, Fachgesellschaften oder Leistungserbringer diese Empfehlungen aufgrund ihrer Qualität und Unabhängigkeit akzeptieren und idealerweise auch umsetzen.

Das Vertrauen in ein solches Expertengremium wird gestärkt, wenn die von ihm formulierten Empfehlungen gemäss internationalen Standards ausgearbeitet werden. Unter anderem sind die Zusammensetzung und die Arbeitsweise wichtig für die Vertrauensbildung.

Eine interdisziplinäre Zusammensetzung sorgt für ausgewogene Entscheidungen, bei denen neben medizinischen und epidemiologischen auch ökonomische, rechtliche und ethische Aspekte sowie auch die Interessen der Patientinnen und Patienten einbezogen werden. Für das Expertengremium Krebsfrüherkennung ist die folgende fachliche Zusammensetzung vorgesehen:

Zusammensetzung Expertengremium Krebsfrüherkennung
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Epidemiologie, Methodologie, Statistik (2 Sitze)
Screening (1 Sitz)
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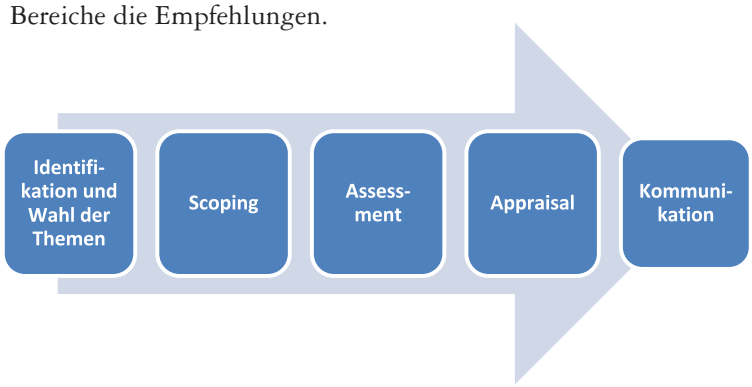
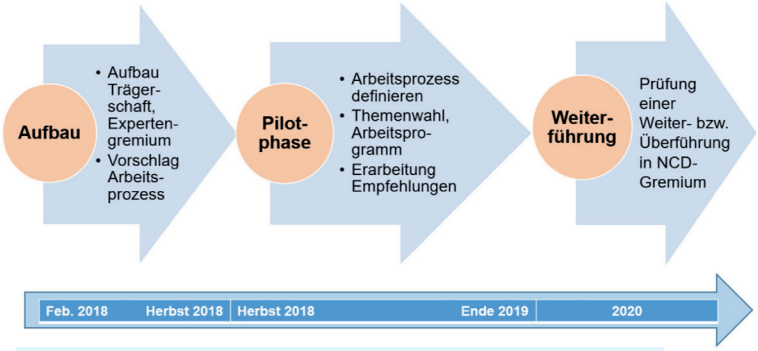
Recht (1 Sitz)
Vertretung Patient/innen (1 Sitz)

Die Arbeitsweise im Gremium orientiert sich an den international etablierten Vorgehensweisen für Bewertungen von medizinischen Verfahren (health technology assessment). Auf der Basis einer systematischen Bewertung der Evidenz nimmt das Expertengremium eine Beurteilung vor und formuliert seine Empfehlung. Empfehlungen für oder gegen Früherkennungsmassnahmen werden in vier Phasen erarbeitet und dann kommuniziert (s. **Abb.**). Zuerst wird entschieden, welche Themen prioritär angegangen werden sollen. In der Phase des so genannten Scopings wird dann die Fragestellung konkretisiert und die Methodik erarbeitet. Danach folgt die Phase des Assessments, während der die Mitglieder des Expertengremiums eine unabhängige Bewertung der Evidenz vornehmen. Schliesslich formuliert das Gremium in der Phase des Appraisals unter Berücksichtigung aller vertretenen Bereiche die Empfehlungen.



Stufenweiser Aufbau des Gremiums

Nach dem Aufbau des Expertengremiums bis im Herbst 2018 werden in einer Pilotphase die Arbeitsweise konkretisiert und erste Empfehlungen erarbeitet. Aufgrund der Erkenntnisse und Erfahrungen in der Pilotphase soll bis zum Ablauf der NSK 2014-2020 entschieden werden, ob und wie ein solches Expertengremium anschliessend weitergeführt werden kann. Der bereits gewählte Präsident, Prof. Marcel Zwahlen vom Institut für Sozial- und Präventivmedizin der Universität Bern, führt das Expertengremium in der Pilotphase. Die Geschäftsstelle ist in der Krebsliga Schweiz angesiedelt. Eine breit abgestützte Trägerschaft (Oncosuisse, BAG, GDK und Public Health Schweiz) hat die Steuerungs- und Aufsichtsfunktion und sichert die Finanzierung.



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Aftercare in Pediatric Oncology in Switzerland – Current State, Challenges and Future Directions

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Abstract

Background

Each year around 300 children are diagnosed with cancer in Switzerland. Given a survival rate of around 85%, 250 childhood cancer survivors are annually entering aftercare. The aim of this research project is to assess the current state and need of aftercare in pediatric oncology in Switzerland by conducting a questionnaire survey. The results are supposed to serve as a basis to establish a Swiss aftercare network fulfilling the needs of the survivors and the treating staff while considering the specific national conditions.

Procedure

A questionnaire was developed containing quantitative and qualitative questions concerning different aspects of aftercare. At each pediatric oncology center either the division head or the responsible staff physician for aftercare were interviewed. Data of all the interviews were integrated and further analyzed to allow quantitative statements.

Results

Aftercare is provided in all of the nine pediatric oncology centers in Switzerland and it is integrated in the regular outpatient clinic setting at most clinics. Consultations are done by pediatric oncologists or pediatricians in training, psychologists and social workers are integrated if needed. There are a lot of similarities between the centers in structural aspects, but several differences concerning individual aftercare plans and transition. The heterogeneity in aftercare among the centers was identified as the main problem.

Conclusions

A survey of experts in aftercare identified several similarities and differences in follow-up treatment and confirms the need for a standardized, well organized aftercare structure for childhood cancer survivors in Switzerland including long-term follow-up care and transition.

Introduction

Aftercare of childhood cancer survivors has been a progressively increasing field within pediatric oncology since treatment improvements have led to a growing number of survivors over the past decades. Progress in cure results in a current international overall 5-year survival rate of around 80% for all childhood malignancies in developed countries [1, 2]. The downside of the increasingly curative treatment are the acute and long term side effects due to treatment's impact on healthy tissue [3]. Adverse treatment-related effects vary in their time of onset, severity and complexity [4]. Over two thirds of survivors have any chronic condition 5 to 14 years after diagnosis, with this number increasing to 77% 15 to 24 years and 85% 25 to 36 years after diagnosis [5, 6]. Thus, there is an increase of morbidity by age leading to functional impairment and activity limitations in the long term [5, 6]. Survivors of

childhood cancer are at risk of adverse treatment effects in aspects of physical, psychological and social development [7-9]. Different organ systems and physiological functions can be or become affected by cancer treatment, such as heart, lung, kidney, thyroid gland, eye, ear, endocrinology, fertility, neurocognition, etc. [5, 10, 11]. Survivors' psychological sequelae include inter alia more depressive symptoms and lower self-esteem [8]. Negative social effects can be isolation or limitation in occupational choice [7]. In terms of work, surveys indicate that survivors are less likely to have a job, are more often limited in the amount or kind of work and more often unable to work because of health problems [12].

A high rate of late effects of cancer and its therapy in combination with a low median age at diagnosis lead to a high burden of long-term disability [13-15], which is besides the individual handicap also a socioeconomic issue [16]. Consequently, providing high-quality aftercare is of vital importance to support survivors in maintaining or gaining a good quality of life [17]. Objectives of survivor surveillance services are early diagnosis and therapy of adverse outcomes as well as provision of survivor education, health promotion advice as well as psychological support [4].

A wide variety of different models of aftercare is described in the literature. Models range from general practitioner only (primary care physician) to shared care, clinic-based follow-up and the telephone/questionnaire model [18, 19]. Within the hospital-based aftercare approach, different models can be distinguished like a specialist nurse-led model, a multidisciplinary clinic, a late effects hospital-based clinic [20] or a joint adult and pediatric clinic for cancer survivorship care [21].

Evidence from comparative evaluations of different models of follow-up treatment is still scarce [20] and the most appropriate models of aftercare are still uncertain [21]. Models of late effect services must be developed that are evidence-based and address the needs of survivors [15].

Preferences and needs of Swiss childhood cancer survivors were explored in several studies by questioning survivors registered in the Swiss childhood cancer registry, most diagnosed with cancer between 1990 and 2005 [22-24].

Preferences of survivors and their parents should be taken into account not only because they are affected but also as this might ensure and increase future attendance in follow-up [22, 25]. What is missing in terms of surveys in Switzerland is an assessment of expert opinions and health care professionals in the field as well as a standardized survey on the structure and organization of aftercare. Consequently, the aims of this study were the following: (1) to describe the current state of aftercare and (2) to assess opinions on challenges and future directions in aftercare in Switzerland by interviewing experts from the nine Swiss pediatric oncology centers.

Materials and Methods

Questionnaire

Since there is no established tool to assess late effect services for childhood cancer survivors in a specific country, our group developed a questionnaire for such an analysis. On the basis of a literature search on survivorship services and models of care combined with practice inputs from clinical expert a questionnaire was developed. In discussion with colleagues from Austria, their currently developed questionnaire on the need of transition and long-term follow-up in pediatric oncology was integrated as well (courtesy of Carina Schneider, Austrian Children's Cancer Aid, 2017).

There are similarities like the population size, geographical conditions and the childhood cancer incidence between the countries of Switzerland and Austria, which legitimate adopting part of the Austrian questionnaire.

The questionnaire contains quantitative as well as qualitative questions and is divided into two main parts. The first part consists of questions about patient numbers and organization of aftercare at the individual center. The second part of the questionnaire aims to assess the target state. Besides questions about current problems and challenges in aftercare locally and nationally, there are questions about the most suitable structure and model of aftercare and transition.

Data Collection / Interviews

All nine pediatric oncology centers in Switzerland (Aarau, Basel, Bern, Zurich, Lucerne, St. Gall, Lausanne, Geneva and Bellinzona) were contacted. Either the division head of pediatric oncology or the responsible staff physician for aftercare were interviewed directly at the local hospital in spring/ summer 2017. Each interview took approximately one hour and all interviews were conducted by the same person. The interviewer documented the answers by notes during the interview.

Data Analysis

The answers of each interview were integrated in a word file in order to obtain a written transcript of each interview. These nine transcripts were then integrated in one single sheet, thus data of all the interviews was combined. Answers were grouped according to the questions of the questionnaire. Data was then analyzed topic-wise by grouping similar answers to each of the questions. The result was a hierarchy of answers ordered by frequency for each of the questions/topics. This allowed us to make quantitative statements.

Ethics Statement

No approval by an ethics committee is required for surveys on aspects of the health care system according to local guidelines on ethics in research concerning humans [26].

Results

Current State

Number of Survivors

Aftercare is provided in all of the nine certified pediatric oncology centers in Switzerland. According to data of the Swiss Childhood Cancer Registry, 1913 survivors have received aftercare at the nine centers in the year 2016. A continuous increase of the number of survivors in aftercare is documented over the course of the last five years in the registry. In 2016, an approximate number of 70 survivors left the structure of aftercare of these centers, i.e. they were transitioned to other health care providers or aftercare was completed.

Reasons for Aftercare

All interviewed experts agree upon the fact that survivors of childhood cancer and cancer treatment need aftercare. The main reason is potentially occurring late effects. According to Swiss experts the aim of aftercare is search for physical as well as psychological late effects as early as possible and to minimize/moderate these effects by suitable treatment. It is also emphasized that over time since completion of treatment, chance of suffering from late effects increases wherefore continuous medical check-ups are vital.

Organization of Aftercare

Structural aspects of aftercare are similar in all nine centers (**Tab. 1**).

On the contrary, there are several organizational aspects varying between the different pediatric oncology centers (**Tab. 2**). Different criteria are used to determine consultation intervals in the different centers. There are various criteria mentioned: recommendations within the treatment studies, survivor's condition, type of disease, risk for harmful effects, current late effects, indication for treatment of late effects. There are also differences in the attending staff's continuity as well as in the multidisciplinary of the team. In about half of the clinics the treating staff changes from one consultation to the next, whereas in the other half the treating staff is continuously the same. Similarly, in about half of the centers multidisciplinary consultations take place if needed. Different criteria are applied to determine the length of aftercare. The following criteria are mentioned most: age, time since diagnosis, type of cancer, survivor's condition, study protocol, survivor's need/wish. In about half of the centers, specialized oncological outpatient clinics for patients with specific diagnoses or problems are already established (e.g. for patients with central nervous system tumors, orthopedic or endocrine problems).

A separate specialized outpatient clinic and program for aftercare, not disease or problem-specific, exists only in one hospital yet. Consultations there are organized with one pediatric oncologist responsible for aftercare, but are not multidisciplinary.

Only in one hospital the Passport for Care® from the Children's Oncology Group (COG) is used as a structured tool including follow-up recommendations for the survivors following transition.

Content of Consultation

Education about potential late effects and the importance of a healthy lifestyle is part of the consultations in all centers.

Tab. 1. Structural Characteristics of Aftercare in Swiss Pediatric Oncology Centers

- Integration of aftercare consultations in the regular oncology outpatient clinic
- Consultation procedure/form: conversation with and physical examination by a doctor, if needed: blood sample, imaging or other diagnostic procedures (ECG, echo, etc.)
- Staff: consultation with a doctor (pediatric oncologist or pediatrician in training), psychologist or social workers consulted if needed
- Treatment initiation in case of diagnosed late effects by involving specific organ specialists
- Scheduling of appointments by the hospital (no initiative by the survivors needed)
- No explicit differentiation of check-ups in a phase of relapse detection and in a phase of aftercare

Tab. 2. Differing Structural Aspects of Aftercare in Swiss Pediatric Oncology Centers

- Criteria for consultation intervals
- Continuity of care of the attending staff
- Implementation of multidisciplinary examinations/consultation hours
- Criteria for length of aftercare
- Specialized outpatient clinic for specific patient populations, e.g. CNS tumor patients
- Separate outpatient clinic for aftercare

Individual Aftercare
Different guidelines for follow-up treatment are applied within the different centers. Aftercare recommendations included in the protocols of the treatment studies as well as COG-guidelines [27] are mentioned most.

Documentation
At least annual reports are done for each survivor. Prior to transition a treatment summary is provided for each survivor. The form and content of this summary differ, e.g. in some of the hospitals the cumulative dose of chemotherapeutic drugs is calculated and mentioned, in others not.

Transition to Adult Medicine
Transition procedures to adult medicine vary between the different Swiss pediatric oncology centers (**Tab. 3**).
Transition of survivors to adult health care providers is integrated in all of the pediatric oncology centers. Additionally, survivors are being prepared and the process of transition is promoted and supported through several talks.
The transition process differs between the centers. In one half of the hospitals transition occurs systematically (each survivor is transitioned to adult medicine), in the other half it occurs demand-oriented, depending on the survivors need or requirements. Furthermore, different criteria to determine the appropriate time for transition and thus for discharge from the pediatric oncology are used in different divisions. Criteria such as survivor's age, survivor's condition (physical/psychological/development), survivor's wish, survivor's current situation in life, time since diagnosis etc. were mentioned. Survivors are transitioned between the age of 16 to 25. The process of transition varies: in one center a joint appointment with the new health care provider from medical oncology/hematology is organized. Survivors are transitioned depending on their conditions and needs either to a general practitioner (GP), an adult oncologist or a specialist without oncology input (e.g. endocrinologist, cardiologist).

Challenges and Future Directions

Current Problems and Challenges in Aftercare
The biggest problem in providing aftercare seems to be the limited resources. Some express to have limited human resources, some have restricted financial resources and some both. As next important issue, the lack of case management was mentioned. It is considered as problematic that there is no responsible person in charge to whom survivors can turn to, like a nurse specialist or a coordinating nurse. Moreover, it is criticized that there is no standardized concept nationally regarding content and documentation of the aftercare clinical visits. Many survivors are still being cared for at the children's hospital in their 20ies and 30ies due to no standardized transition process.

Standardized Tool
Most experts consider a survivorship passport to be the best tool to summarize the patient's treatment information and to generate an individual aftercare plan.

Best Aftercare Model
The interviewed experts have different ideas about the most suitable model of aftercare for Switzerland. Some experts think that aftercare should be conducted in the same clinic as the cancer treatment, others think that a different setting is needed. It is suggested that a board of specialists should be created to develop criteria for Swiss aftercare. In a second step, this board could also discuss about the follow-up treatment of complex cases, e.g. by videoconference. The board of specialists can be subdivided into smaller networks of specialists responsible for the different cultural and language regions.
The interviewees identify the pediatric oncologist as the person who should lead the aftercare. A specialized nurse is mentioned several times as well. Some regard social workers, some psychologists as an inherent part of the screening staff, others express that these specialists can be referred to if needed.
Concerning transition, experts agree that survivors should be transitioned to adult medicine but disagree about the best institution for young adult survivors. Establishing specialized outpatient clinics for aftercare for children and adolescent survivors as well as specialized clinics for long-term aftercare for adult survivors was mentioned twice. GPs, specialized office-based adult oncologists and adult oncologists in a hospital setting are considered as the best responsible physician following transition.

Tab. 3. Similar and Differing Aspects in the Process of Transition in Swiss Pediatric Oncology Centers

Similarities	Differences
• Realization of transition to adult medicine	• Form of transition
• Survivor preparation for transition	• Criteria for transition
	• Process of transition
	• Staff survivors are transitioned to

Discussion

Long-term aftercare is provided in all pediatric oncology centers in Switzerland and is integrated in the regular oncological outpatient clinics or disease specific clinics. Only one specialized outpatient clinic for aftercare of childhood cancer survivors has been established so far. This lack of separate and specialized aftercare clinics exists in other European countries. In a recent European survey, only 38% of the hospitals performing follow-up care report having a separate dedicated long-term follow-up clinic [28]. In an American survey 59% of the assessed centers indicate to have a specialist late effects program [29] and in a Canadian survey 71% have a formal program or clinic dedicated to aftercare [30]. Consultation procedures are similar in all Swiss clinics and there are different outpatient clinics for specific disease groups (e.g. survivors of brain tumors) in more than half. Follow-up consultations are undertaken by pediatric oncologists or pediatricians in training. Psychologists and social workers are only consulted if needed. There are no coordinating nurses or nurse practitioners involved in aftercare management. In fact, these professionals are still very rare in the Swiss health care system in general. There are differences between the Swiss centers in length of follow-up, in the staff's continuity and multidisciplinarity and in the criteria for control intervals.
In a questionnaire survey of follow-up programs for European childhood cancer survivors many similar results are found as to structure, staff and content: most long-term follow-up clinics for pediatric survivors were situated in pediatric hospitals and run by a pediatric oncologist [31]. Nurses are involved in less than half of the institutions. The authors determine a lack of dedicated nurse practitioners. As to the content of surveillance services, the majority reports using guidelines and providing education about the disease, treatment, late effects and health behavior.

The following elements are considered to be contributing to high quality aftercare: education, guidelines, survivorship care plan, treatment summary, transition [18, 19]. Education is already part of long-term care in all Swiss clinics but it could certainly be improved, according to the survivors by also providing more written and personalized information. Possible educational material could be risk-adapted handouts for different patient groups or checklists with information on different topics as suggested in the Scottish guidelines [32]. Our results indicate that Swiss experts turn to different guidelines for information to optimize individual aftercare. International evidence-based long-term follow-up guidelines that are being developed by the International Guideline Harmonization Group (IGHG) are much needed also in Switzerland in order to homogenize aftercare [33].

A treatment summary is prepared in all Swiss clinics, which mostly contains some recommendations about follow-up care as well. Only in one center, individual aftercare plans are generated for survivors by using the Passport of Care®. In an Internet survey study of US clinics, 68% of institutions provide survivors with a copy of their survivorship care plan as well as of their oncology treatment summary [29]. The implementation of a survivorship passport in all of the Swiss pediatric oncology clinics is planned for the near future, which will be a step towards more standardized as well as individualized aftercare.
Transition is regarded as a critical step in the process of aftercare for survivors since the change from pediatric to adult health care system is accompanied not only by a change of the treating staff but survivors are also faced with the expectation that patients assume the primary responsibility of their own care [34, 35]. All interviewed Swiss experts declare that transition takes place at their hospital. The physicians invest time in the transition process of the survivors so that they gain further understanding and knowledge of their treatment and potential treatment-related complications, which is essential for their long-term aftercare. The form, criteria and date of transition as well as the staff, survivors are transitioned to, differ between the Swiss pediatric centers and are topics for future discussion and potential harmonization. Survivors are most often and approximately equally often transitioned to a GP or an adult oncologist, which is very similar to the rest of Europe where 70% of institutions discharged pediatric survivors, mostly to GPs (42%), adult oncologists (37%) or a transition program (18%) [31].

The most relevant local problems in Swiss pediatric oncology centers providing aftercare are limited human and financial resources. These are similar to the difficulties encountered in other European countries which are lack of human resources, time, funding and understanding by colleagues [31].
Interviewed experts identify the heterogeneity in different aspects of aftercare as the main problem and regarded developing an appropriate model for Swiss aftercare as important. A lack of a national strategy or standards is also stated by 61% of the respondent countries in a recent European survey [28]. Swiss experts' opinions about the most suitable model differ wherefore a profound exchange is needed to successfully develop a model widely accepted. Concerning the differences in various areas of Swiss aftercare, it has to be discussed further which aspects are important to be unified and which not. Regulations und guidelines should not be too forced since individually tailored decisions for the treatment of a specific patient are indispensable and remain essential in survivorship services [27, 36]. A working group for aftercare addressing these topics has already been established in Switzerland.

According to Skinner et al. the most suitable organizational model for long-term follow-up depends on factors like local resources, expertise and interests, center size and regional geography [4]. All of these aspects have to be taken into account for a possible future concept for Swiss aftercare. The population of childhood cancer survivors is growing in Switzerland, thus long-term aftercare by pediatric oncologists or even well-organized survivorship clinics might not be manageable in the long run, so that other models need to be discussed. This issue has also been frequently discussed in other countries lately [18, 25, 37]. Traditional models of hospital-based long-term aftercare may also not be sustainable and clinically justified in all cases [19, 38]. Researchers are increasingly working on the concept of a risk-stratified approach where survivors' follow-up care is adapted depending on diagnosis and therapy [25, 32, 39]. Low-risk survivors could be transitioned to GP-led follow-up and for high-risk survivors specialist care in long-term outpatient clinics would make sense [24, 25].

This is the first assessment of the current state of aftercare in Switzerland as well as of experts' opinion on different aspects of aftercare.
A limitation of this study is the large heterogeneity of answers on certain questions due to the open question format resulting in a challenging analysis and reporting of results. Additionally, it could be that answers in the interviews were adapted due to social desirability, meaning that the interviewees confirmed some questions because they know that the aspects under question (like a service or an aspect of treatment) are considered as positive by the clinical and scientific community [31].
Based on the findings of this study, future efforts and research should focus on working out best practices for Swiss aftercare including inputs and needs from survivors, parents as well as health care professionals. The results of our study indicate that transition and long-term follow-up of adult survivors are areas of need and potential for development. Possible future concepts for aftercare of Swiss childhood cancer survivors are to account for the fact of four different language areas (German, French, Italian, Rätoromansch) as well as the different size of pediatric oncology centers in Switzerland.

Conclusion

Survivorship services including transition are available in all Swiss pediatric oncology centers. Despite many structural similarities in the organization of aftercare, there is a lack of formal long-term follow-up programs or clinics. Inconsistencies exist in important areas like in the use of guidelines, standardized individual survivorship care plans and in the process of transition. Besides implementation of a survivorship passport and international follow up guidelines, a concept of adequate aftercare is needed to homogenize aftercare for childhood cancer survivors in Switzerland.

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Incidence-based Mortality Trends for Thyroid Cancer: Is there a «true» Increase in Incidence of Thyroid Cancer in Switzerland?

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Introduction

Thyroid cancer is the most important cancer among endocrine tumors. In Switzerland it accounts for less than 3% of all invasive cancers in women and for less than 1% in men. This corresponds yearly to 650 (490 women, 160 men) new cases of thyroid cancer and 60 (40 women, 20 men) deaths from thyroid cancer during 2008-2012. The yearly age standardized incidence rate in this period accounted for 11.0 and 3.6 new cases per 100'000 among women and men, respectively. Since the year 1983 this rate is only slightly increasing for men but doubled for women [1].

Similar trends are seen in other European countries, in America and Asia, which are accompanied by improving survival rates [2, 3]. In Switzerland, the 10-year survival rates between 1998 and 2012 increased too, from 79% to 88% among women and to 85% among men, respectively. In comparison to ten other European countries, the survival rate in Switzerland ranks 6th for women and 4th for men [1, 4].

The debate about the underlying causes of the observed dramatic increase in incident thyroid cancer is still ongoing. Some groups claim that the increase is only due to overdiagnosis of mainly indolent cancers of small sizes, which untreated would probably not result in death and not even in symptoms [5]. This would naturally also increase thyroid cancer survival rates. Recently, the impact of overdiagnosis possibly underlying the worldwide thyroid-cancer epidemic was quantified by comparing observed rates vs. rates expected without overdiagnosis for thyroid cancer from different countries [3]. Overall, more than 470,000 women and 90,000 men may have been overdiagnosed with thyroid cancer over two decades in the 12 countries analyzed [3]. On the other hand, some reported a «true» increase in thyroid cancer incident cases showing a positive trend in «incidence-based» mortality during 1994-2004 in the United States [6]. Therefore more studies are needed across different countries to better understand the various underlying causes of the dramatic increase in thyroid-cancer incidence in the last decades.

A recent study in Switzerland showed a large increase in the incidence of thyroid cancer during 1998-2012, limited to papillary and early stage tumors, with a three- to fourfold parallel increase in thyroidectomy. The mortality slightly decreased. The authors postulate that a substantial and growing part of the detected thyroid cancers are overdiagnosed and overtreated [7].

In our study, we focus on «incidence-based» mortality of thyroid cancer by histologic subtypes to evaluate if a part of the thyroid cancer increase observed in Switzerland could be explained by a «true» increase as it was shown by Lim et al. for the United States [6]. Moreover, we update and extend the previously reported incidence trends of thyroid cancer by sex, age and language region.

Methods

The Foundation National Institute of Cancer Epidemiology and Registration (NICER) manages the population-based national cancer dataset, with the purpose of providing comprehensive cancer surveillance for Switzerland, as well as supporting epidemiological cancer research [8]. Population-based cantonal cancer registries collect data directly from patients' medical records and transmit a defined and pseudonymized subset of the information to NICER. Diagnoses from 1988 to 2014 in thirteen cantons where cancer registration covered at least 19 consecutive years (ZH, GR, GL, SG, AR, AI, BS, BL, VD, NE, VS, GE, and TI) are included in this report. The first eight cantons represented the German-speaking part of Switzerland, and the remaining five cantons the French/Italian-speaking part. The respective cancer registries cover about 60% of the Swiss population. Case counts for whole Switzerland are extrapolations by sex, age, tumor group, and Swiss language region.

Selection criteria were all primary tumors of malignant behavior with topography code C73 from the International Classification of Diseases for Oncology, third edition (ICD-O-3) [9]. Excluded are all systemic tumors (ICD-O-3 morphology code M9580 and higher). Almost all diagnoses were confirmed microscopically (>98%). We differentiated between papillary carcinoma (M8050, M8260,

M8340-M8344, M8350, M8450, M8452, M8453, M8460), follicular carcinoma (M8290, M8330-M8333, M8335), medullary carcinoma (M8345, M8510, M8512, M8513), anaplastic carcinoma (M8020-M8022, M8030-M8035), other specified morphologies (M8041, M8043, M8051, M8052, M8070-M8072, M8140, M8190, M8230, M8231, M8240, M8246, M8250, M8310, M8337, M8346, M8347, M8430, M8560, M8574, M8589, M8680, M8800, M8801, M8810, M8830, M8890, M8980, M9120, M9130, M9150), and unspecified cancer types (M8000-M8005, M8010-M8012).

Incidence rates are expressed as N cases per 100,000 person-years, and age-adjustment of rates for all ages combined, as well as within age groups, was based on the EU standard population [10]. The study is observational, thus confidence intervals should only be interpreted as rough descriptors of uncertainty [11].

Incidence-based thyroid cancer mortality trends are based on cantons and years of death with fewer than 15% missing information on the cause of death for registered cancer patients. These included 8 cantons (GR, GL, SG, AR, AI, VS, GE, and TI) and death years 2000-2014. For each canton, there were at least 5 years of incidence registration before causes of death analysis started in 2000. Just 0.3% of cases were based on death certificates only, i.e. the true incidence date was unknown and has been set to the day of death.

Annual percentage changes (APC) were estimated using a heteroscedastic simple linear model for logarithmic transformed age-standardized mortality rates implemented in the Joinpoint Regression Program v4.4.0.0 [12].

Results

A) Incidence-based mortality trends (IBM)

The analysis for trends in incidence-based mortality rates for the mortality years 2000-2014 is shown in **Table 1**, **2** and **Figure 1**.

Over 98% of thyroid cancer diagnoses were confirmed by microscopy. Histology of thyroid cancer was first divided into the following morphologic subgroups: papillary, follicular, medullary, anaplastic and unspecified histology and then constricted to three groups: papillary, non-papillary (follicular, medullary, anaplastic) and unspecified histology to achieve enough statistical power.

In our data sample, a total of 992 patients diagnosed with thyroid cancer (C73, ICD-10) have died. Half of these patients died from thyroid cancer and nearly half of other causes: the cause of death (CoD) was thyroid cancer (C73) in 486 (49.0%) patients, or 176 men (17.7%) and 310 women (31.3%) (**Tab. 1**). CoD was not C73 in 472 (47.6%) patients, and was unknown in only 34 (3.4%) patients (**Tab. 1**).

	CoD not C73		CoD C73		CoD Unknown		
Thyroid Cancer (C73) Histologies	Men	Women	Men	Women	Men	Women	Total
	N Counts						
Papillary	70	184	48	80	4	8	394
Non-papillary	58	150	118	192	12	10	540
Unspecific histology	6	4	10	38	0	0	58
All histologies	134	338	176	310	16	18	**992**
	Proportion (%) of all histologies and all Causes of Death (CoD)						
Papillary	7.1	18.5	4.8	8.1	0.4	0.8	39.7
Non-papillary	5.8	15.1	11.9	19.4	1.2	1.0	54.4
Unspecific histology	0.6	0.4	1.0	3.8	0.0	0.0	5.8
All histologies	13.5	34.1	17.7	31.3	1.6	1.8	**100**
	Proportion (%) of all C73 deaths						
Papillary			9.9	16.5			
Non-papillary			24.3	39.5			
Unspecific histology			2.1	7.8			
All histologies			36.2	63.8			

Tab. 1. Number of available Swiss thyroid cancer cases (C73) for the analysis for trends in incidence-based mortality rates. Data were used from eight cantons (SG/AR/AI, GR/GL, TI, VS, GE) for the death years 2000-2014 due to missing or incomplete data in other Swiss registries. CoD=cause of death.

There were 394 (39.7%) patients with papillary carcinoma, 540 (54.4%) patients with non-papillary carcinoma, and only 58 (5.8%) patients with unspecific types of thyroid cancer, indicating good quality data. More than a quarter (26.4%) of the patients who died from thyroid cancer (C73) were previously diagnosed by the histologic type of papillary carcinoma, 63.8% by non-papillary histology and 9.9% by unspecified histology type of thyroid cancer (**Tab. 1**).

The distribution patterns of these three different histology groups among those who died from thyroid cancer were very similar over the analyzed time period from 2000-2014. Histology-specific causes of death in the period 2000-2004 were 24.1%, 66.7%, and 9.2% for papillary, non-papillary, and unspecific thyroid cancer, respectively, and 24.1%, 66.3%, and 9.6% in the period 2010-2014, respectively [data not shown].

Figure 1 shows age-standardized incidence-based mortality (IBM) rates of thyroid cancer death by year of death and by histologic type for Switzerland, based on a subset of eight cantons. The histology-based mortality trends for papillary and non-papillary histologic subtypes are interpreted as representative for whole Switzerland because the IBM trend for all histologic types was identical to the mortality trend for thyroid cancer for the death years 1988 to 2014 in the official Statistic of the Federal Office (FSO) (**Fig. 1**).

Histologic type	Statistics*	APC** [%]	95% CI
Papillary	IBM	-0.4	(-6.3, 5.9)
Non-Papillary	IBM	-3.6	(-6.8, -0.3)
All histologies	IBM	-3.0	(-6.0, 0.0)
All histologies	FSO	-3.6	(-4.2, -3.1)

Tab. 2. Thyroid cancer as principle cause of death for different histologic types. *Statistics: IBM: Incidence-based mortality rates based on deaths during 2000-2014 and cases diagnosed 1996-2014, in a subset of 8 Swiss cantons; FSO: Mortality rates from the official vital statistics (FSO) are based on deaths during 1996-2014 from all 26 Swiss cantons. **APC: Annual percentage changes in age-standardized mortality rates.

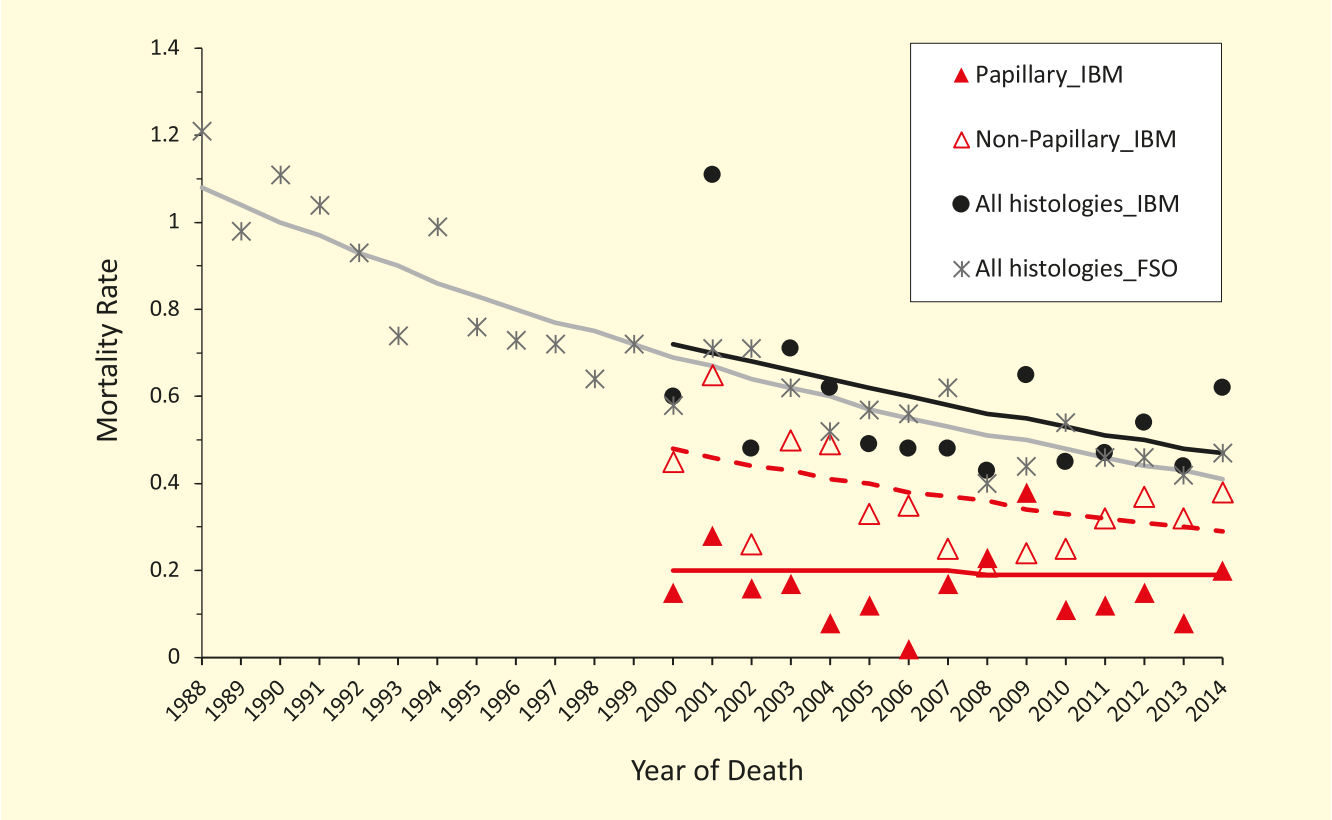

Fig. 1. Thyroid cancer as principle cause of death (CoD) for different histologic types. Age-standardized incidence-based mortality rates (IBM) are based on deaths during 2000-2014 and cases diagnosed during 1996-2014, in a subset of eight Swiss cantons. Mortality rates from the official vital statistics (FSO) are based on deaths during 1988-2014 from all 26 Swiss cantons.

The time trend for mortality of thyroid cancer over all histologies is steadily decreasing (negative), and a positive trend for the papillary histologic type alone could not be observed with the actual data from Swiss Cancer Registries. The annual percentage change of papillary IBM was -0.4 and not significantly different from zero (95%CI: -6.3, +5.9; **Tab. 2**). Due to limited data for Switzerland this analysis could not be done separately by stage of thyroid tumor. Nevertheless, the current analyses for Switzerland do not point towards a positive IBM-trend and therefore do not confirm the U.S.-results for a true incidence increase in thyroid cancer in Switzerland.

B) Incidence trends by language region (French/ Italian-speaking vs. German-speaking regions)

Table 3 provides estimates for incidence and mortality rate trends for thyroid cancer separate for the two different Swiss language regions: cantons with predominantly French and Italian speaking residents (F/I region) and cantons with predominantly German speaking residents (G region). Age-standardized (European population) incidence rates per 100,000 for all morphologies combined ranges from 3.39 in the first period (1988-90) to 10.85 in the last period (2012-14) among French/Italian speaking cantons and from 4.23 to 7.42 among German speaking cantons in Switzerland

Region	Period	Women				Men				Total			
		N diagnoses*	IR# adjusted	N deaths	MR## adjusted	N diagnoses*	IR# adjusted	N deaths	MR## adjusted	N diagnoses*	IR# adjusted	N deaths	MR## adjusted
SL: French/Italian language region	1988-1990	159	4.70	40	0.84	56	1.95	17	0.61	215	3.39	57	0.77
	1991-1993	186	5.39	43	0.92	47	1.56	22	0.72	233	3.59	65	0.84
	1994-1996	197	5.60	35	0.64	63	2.06	14	0.44	261	3.90	49	0.58
	1997-1999	226	6.25	44	0.78	82	2.55	15	0.44	308	4.47	59	0.65
	2000-2002	270	7.39	43	0.78	102	3.06	26	0.75	372	5.29	69	0.77
	2003-2005	318	8.68	26	0.46	129	3.78	17	0.43	447	6.30	43	0.44
	2006-2008	372	9.83	25	0.34	135	3.84	21	0.52	508	6.91	46	0.43
	2009-2011	560	14.01	27	0.40	157	4.13	23	0.54	718	9.18	50	0.48
	2012-2014	636	15.63	36	0.45	239	5.97	21	0.44	876	10.85	57	0.46
SA: German language region	1988-1990	496	5.66	161	1.30	190	2.67	83	1.08	687	4.23	244	1.23
	1991-1993	484	5.54	116	0.95	213	2.88	69	0.88	698	4.25	185	0.93
	1994-1996	639	7.30	124	0.95	235	3.04	68	0.86	877	5.24	192	0.92
	1997-1999	594	6.68	106	0.73	199	2.39	55	0.65	795	4.59	161	0.71
	2000-2002	646	7.11	100	0.72	213	2.52	43	0.48	861	4.84	143	0.62
	2003-2005	687	7.57	102	0.65	242	2.85	52	0.56	930	5.25	154	0.62
	2006-2008	887	9.54	90	0.57	299	3.32	54	0.53	1187	6.47	144	0.56
	2009-2011	948	9.97	96	0.53	378	4.00	47	0.42	1327	6.97	143	0.48
	2012-2014	1010	10.52	67	0.35	432	4.41	60	0.52	1441	7.42	127	0.44
CH	1988-1990	654	5.39	201	1.17	246	2.46	100	0.95	902	3.99	301	1.10
	1991-1993	670	5.50	159	0.95	259	2.50	91	0.84	931	4.07	250	0.90
	1994-1996	837	6.81	159	0.86	298	2.76	82	0.74	1137	4.85	241	0.82
	1997-1999	820	6.56	150	0.74	280	2.43	70	0.59	1102	4.56	220	0.69
	2000-2002	917	7.19	143	0.74	315	2.67	69	0.55	1233	4.97	212	0.67
	2003-2005	1005	7.89	128	0.60	370	3.12	69	0.52	1377	5.55	197	0.57
	2006-2008	1259	9.62	115	0.51	434	3.47	75	0.53	1695	6.59	190	0.52
	2009-2011	1508	11.14	123	0.49	536	4.04	70	0.45	2045	7.61	193	0.48
	2012-2014	1646	11.99	103	0.38	671	4.86	81	0.50	2317	8.41	184	0.45

Tab. 3. Number of thyroid cancer cases (N diagnoses), incidence rates (IR), number of death (N deaths) and mortality rates (MR) in Switzerland by language region, sex and time-period. SL: cantons with predominantly French and Italian speaking residents (GE, NE, VD, VS, TI). SA: cantons with predominantly German speaking residents (BS/BL, GR/GL SG/AR/AI, ZH). CH: Whole Switzerland. * Estimate for whole Switzerland. # Age-adjusted incidence rate (per 100,000). ## Age-adjusted mortality rate (per 100,000).

(**Tab. 3**). The estimated mortality rates are small as expected and almost stable resp. slightly decreasing over time.
The within-country geographical comparisons are depicted also in **Figure 2**. The much steeper thyroid cancer incidence increase in the F/I speaking cantons compared to the G region during the last 25 years is illustrated predominantly in the curve for papillary thyroid cancer incidence in women in this region (**Fig. 2**): the directly adjusted rate for F/I cantons is quadrupled in this group from 1988-2014, whereas it is tripled in the G region.

C) Incidence trends of papillary thyroid carcinoma by sex, age and time period

To further evaluate the observed steep increase in thyroid cancer over time of predominantly papillary histologic type we compared age-specific incidence rates by sex in the first time period (1988-90) and the last (2012-14) (**Fig. 3**).
Figure 3 demonstrates the large sex difference already seen in the overall incidence trends for thyroid cancer of combined histology types consistent with the world-wide observations: thyroid cancer is mainly a female cancer and has increased mainly in women with papillary histologic type over the last decades.

Whereas the youngest (age 0-19) and oldest (age 80-89) age group of analyzed women at the time of diagnosis have the same incidence rates today as 25 years ago, there is a great difference for the middle aged women, with a peak for the 40-60 years old. In the time period from 2012-14 there are around 4-times more female patients

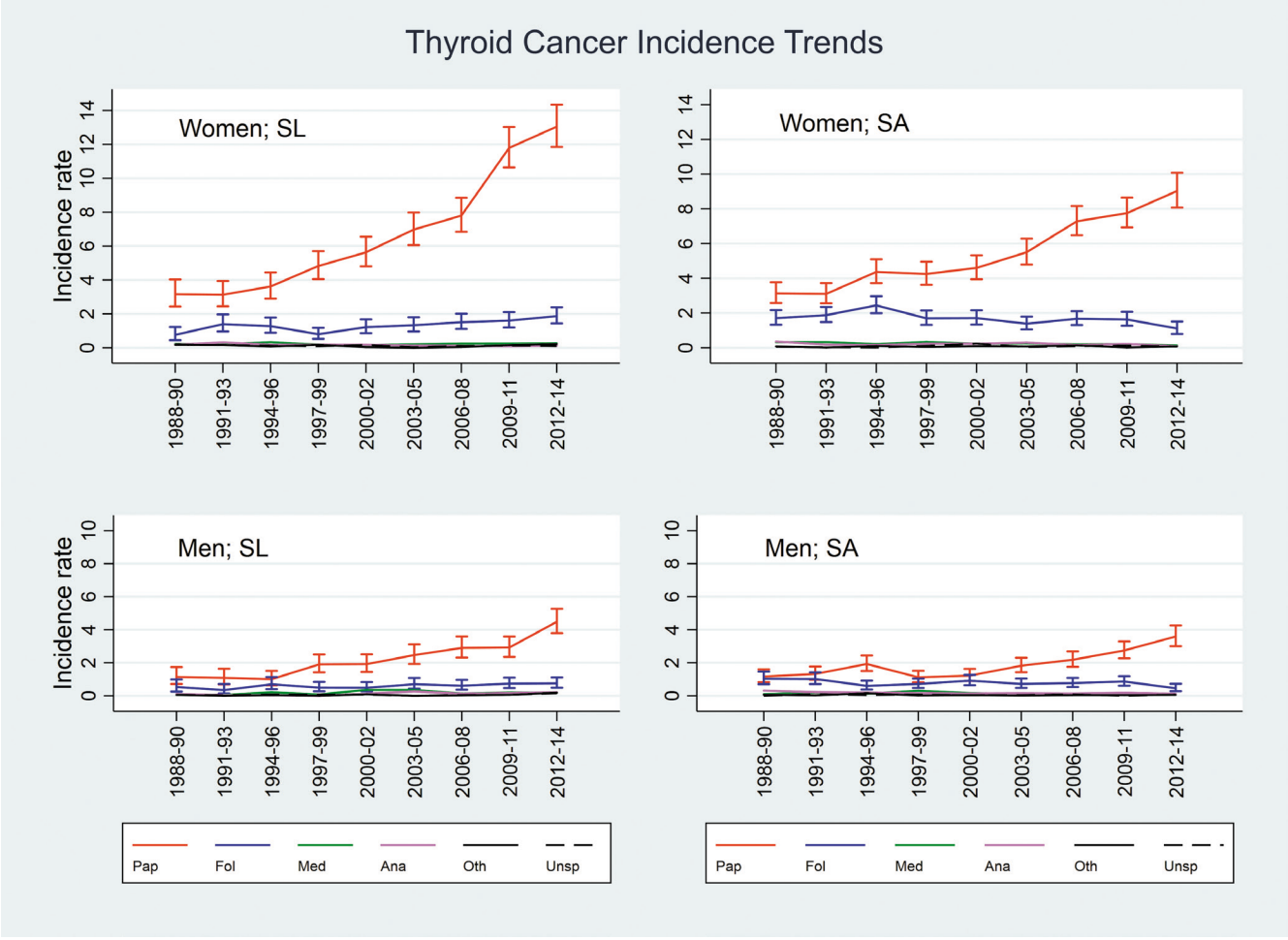

Fig. 2. Swiss thyroid cancer incidence trends by language region, sex, time period and histology types. SL: French/Italian language region, SA: German language region. Pap: papillary carcinoma, Fol: follicular adenocarcinoma, Med: medullary carcinoma, Ana: anaplastic carcinoma, Oth: other specific cancer types, Unspec: un-/poorly specified cancer. Incidence graphs for Pap and Fol are plotted with 95% confidence intervals. Included F/I speaking cantons: GE, NE, VD, VS, TI. German-speaking cantons: BS/BL, GR/GL SG/AR/AI, ZH. Incidence rates are age-standardized based on the EU standard population.

diagnosed from thyroid cancer at the age of 40-60 years than 25 years ago. Similar effects are seen for men, but much less prominent.

Discussion

Data registered by the Cantonal Cancer Registries (F/I speaking cantons: GE, NE, VD, VS, TI and German-speaking cantons: BS/BL, GR/GL SG/AR/AI, ZH) and aggregated by NICER (National Institute for Cancer Epidemiology and Registration) from the incidence years 1988-2014 have been used to analyze trends in thyroid cancer incidence and mortality by sex, age, histology, and language region.

The findings are consistent with other Swiss reports and studies [1, 7, 15, 16, 17] and confirm the world-wide massive upward trend of thyroid cancer incidence and concomitant slight decrease of mortality trends during the last decades. The underlying mechanisms of this observation are not yet fully understood, but it is widely accepted that probably the overdiagnosis of indolent, non-lethal cancers picked up by screening are responsible for it [5]. A recent comment & response in *JAMA* [13, 14] brought up the question again: is there at least a partial «true» increase in thyroid cancer to be concerned about? Because Lim et al. [6] could show by means of a novel method of analysis for thyroid cancer mortality by tumor characteristics (histologic type and stage) at diagnosis that among patients in the United States diagnosed with thyroid cancer from 1974-2013, the overall incidence of thyroid cancer increased 3% annually, with increases in the incidence rate and thyroid cancer mortality rate for papillary thyroid cancer. The authors claim that these findings are consistent with a true increase in the occurrence of thyroid cancer in the United States.

Therefore we applied the method of Lim et al [6] in our current study to the available data in Switzerland. Due to

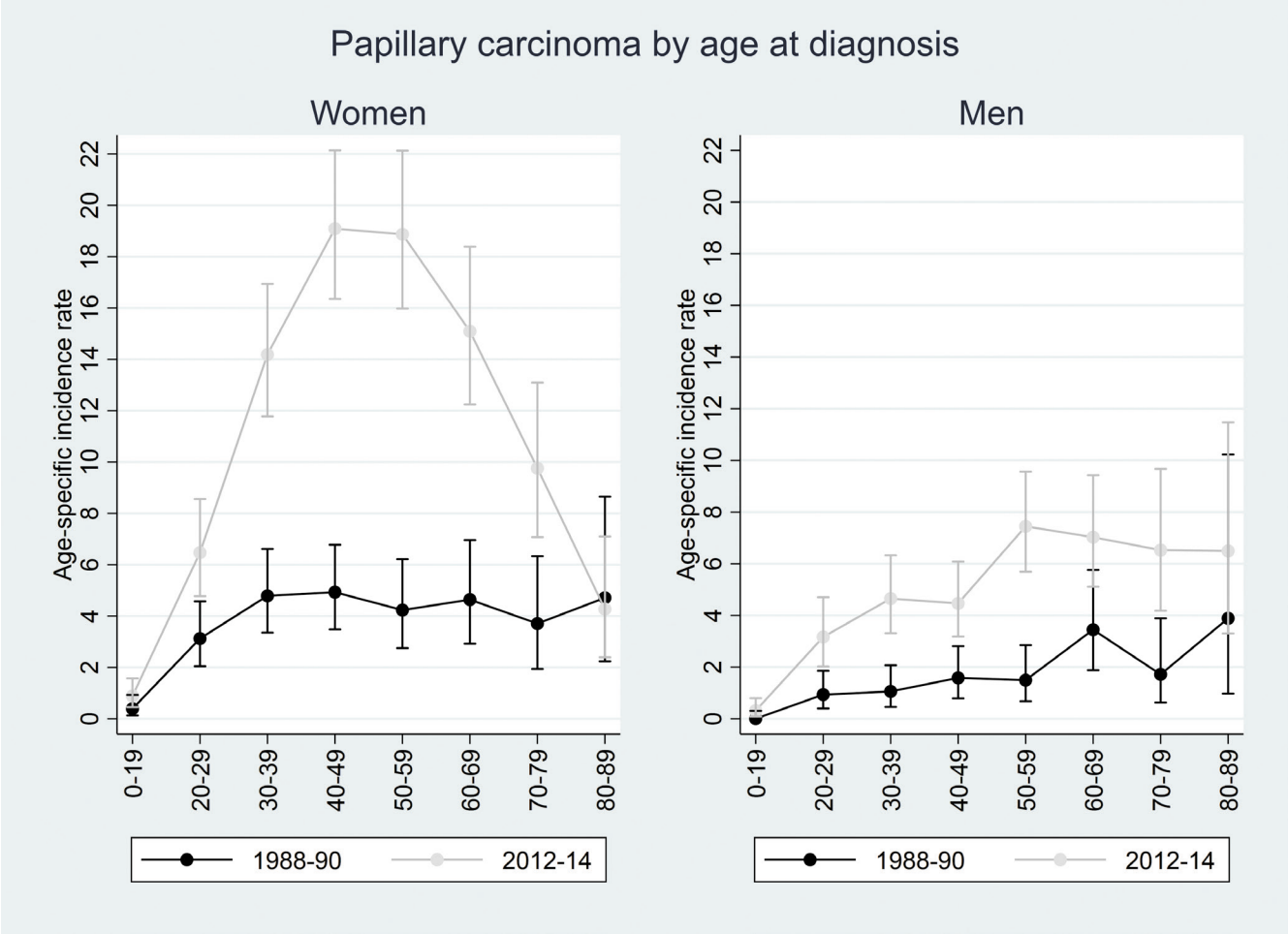

Fig. 3. Age-specific incidence rates of papillary thyroid cancer by sex, age at diagnosis and time period.

incomplete death data and to prevent the effect of underestimation, as usually found in the first years of registration, we limited our analyses to data of eight cantons (SG/AR/AI, GR/GL, TI, VS, GE) and the death years 2000-2014. We could build the histologic groups of papillary and non-papillary (medullary, follicular, anaplastic) but could not discern further subgroups as sex, or language group.

The results of the Swiss analysis could not reproduce the upward trend in mortality rates for the papillary type of thyroid cancer as found in the United States which would indicate a true increase in thyroid cancer incidence. Although a small doubt for a weak «true» effect remains because the available Swiss data had not enough statistical power to detect a very small difference and could not be analyzed separately by tumor stage. The U.S.-data analysis had shown the highest positive effect for distant stage tumors. Nevertheless, the actual evidence from the Swiss data does not reveal it, thus indicating overdiagnosis as main cause of the incident thyroid cancer increase.

An earlier study in the Swiss canton of Geneva already examined possible «artificial» factors, in contrast to a «true» increase, for the increased incidence of papillary thyroid cancer for the diagnosis years of 1970-1998. It depicts that this increase seems mainly to be due to changes in histological diagnostic criteria (follicular->papillary) and, to a lesser extent, to increased diagnostic activity [15]. The authors conclude that implementation of iodine supplementation in iodine deficiency areas should not be stopped. Similar results were shown for thyroid cancer increase for both genders in the Swiss canton of Vaud [16]. Moreover, a birth cohort study indicated similar results for thyroid cancer in Switzerland and could not definitively exclude a Chernobyl accident effect (no non-liner effect on all cohorts could be shown) [17]. Our current study confirms the above mentioned explanations.

Furthermore, our results show that the overall age-adjusted incidence rates of thyroid cancer have been increasing in Switzerland mainly for papillary carcinoma, with the greatest increase among young and middle-aged women. Today there are around four times more female patients diagnosed from thyroid cancer at the age of 40-60 years than 25 years ago (**Fig. 3**). This is in accordance to the results from other high-income countries [3, 18] and the cohort effect described by Montanaro et al. for Switzerland [17]. Plausible explanations could be the improvement in diagnostic techniques, higher awareness and changes in diagnostic criteria.

Besides the enormous differences in thyroid cancer incidence by sex and age, prominent differences by language regions were observed. Overall the French/Italian-speaking cantons (F/I region) had higher age-adjusted incidence rates for thyroid cancer for both sexes in the recent years than German-speaking cantons (G region). This difference is negligible for men, but prominent for women, mainly for the papillary histologic type.
The language regional difference in the increasing incidence trend and overdiagnosis of thyroid cancer could partly be explained by the difference in the frequency of using imaging tests, which are important in thyroid cancer detection. In the F/I region imaging tests as ultrasound, computerized tomography scans and magnetic resonance imaging are in general applied more frequently than in the G region, as analysis of Swiss health insurance data in a report issued by the Federal Office of Public Health (FOPH) revealed recently [19]. Moreover, there are a number of Swiss studies and reports pointing out the cultural differences in health behavior and prevention [20, 21].

Conclusion

Our current study supports the hypothesis of overdiagnosis as main explanation for the thyroid cancer incidence increase in Switzerland observed in the last decades, but does not definitively exclude a partly true increase. Therefore further studies with increasing power are needed to minimize the public health burden of overdiagnosis discerning the lethal from the indolent, non-lethal thyroid carcinomas and to determine any possible relations to specific exposures (e.g. ionizing events) in Switzerland due to a partly true increase of thyroid cancer.

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For additional information on cancer in Switzerland, see the NICER website at http://nicer.org/

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30 Jahre Onkologiepflege Schweiz

Irène Bachmann-Mettler, Präsidentin Onkologiepflege Schweiz

Für einmal standen die Gründerinnen, Wegbeleiterinnen und Wegbegleiter der Onkologiepflege Schweiz (OPS) im Vordergrund der Jubiläumsfeier, die aus Anlass zum 30 jährigen Bestehen stattgefunden hat. Zahlreiche Gäste und Mitglieder der OPS waren dabei, als die Pionierinnen der Onkologiepflege feierlich geehrt und die Geschichte der Onkologiepflege Schweiz gewürdigt wurden.

Ehrung von Pionierinnen der Onkologiepflege

Stellvertretend für viele andere Pionierinnen und Pioniere, welche die Onkologiepflege in der Schweiz in der Praxis und in der Vereinsarbeit aufgebaut und entwickelt haben, wurde Anita Margulies, Zürich, Yvonne Willems Cavalli, Ascona, und Lucienne Bigler-Perrotin, Genève, für ihre langjährigen und ausserordentlichen Verdienste die Ehrenmitgliedschaft der Onkologiepflege Schweiz (OPS) verliehen.

Anita Margulies ist nicht nur in der Schweiz, sondern auch international eine fachlich anerkannte Expertin in Onkologiepflege. Während über 40 Jahren engagierte sie sich für den Aufbau und die Weiterentwicklung der Onkologiepflege am Universitätsspital Zürich und wurde bald eine Referenzperson und Dozentin für fachspezifische und neue Themen. Seit den 90er Jahren war sie Mitglied der Interessengruppe Onkologiepflege und von 2002-2011 Vorstandsmitglied der Onkologiepflege Schweiz. Einer ihrer grössten Verdienste als Vorstandsmitglied war der Aufbau von Fortbildungsveranstaltungen für Pflegefachpersonen in der Onkologie. 2006 startete sie mit vier Fortbildungen, heute sind es über 30 Veranstaltungen mit über 500 Teilnehmenden pro Jahr. Unter ihrer Leitung gelang es der Gruppe Fortbildungen/OPS, attraktive, praxisbezogene sowie thematisch breit gefächerte wie auch wissenschaftlich fundierte Fortbildungen anzubieten. Ab 2017 hat sie die Leitung der Gruppe an Silvia Rusch weitergegeben.

Anita Margulies

Weitere Meilensteine im Lebenswerk von Anita Margulies sind, unter vielen anderen, folgende Leistungen im Rahmen ihrer Tätigkeit für die OPS:

- Co-Autorin: Leitfaden Orale Mukositis
- Mitglied der Arbeitsgruppe Adhärenz Orale Tumortherapie OPS/SGMO: Federführend in der Erarbeitung der Medikamentenmerkblätter «Orale Tumortherapie für Patientinnen und Patienten»
- Erarbeitung der Grundlagen und Kompetenzen für die Höhere Eidgenössische Fachprüfung, OdaSante

Anerkennung und einen hohen Bekanntheitsgrad erlangte Anita Margulies auch durch ihre Publikationen als Co-Herausgeberin der Bücher «Onkologische Krankenpflege» und «Medikamente in der Tumortherapie».

Auf dem internationalen Parkett trat Anita Margulies beispielsweise als Organisatorin und Referentin an Kongressen und Schulungsprogrammen auf und war Vorstandsmitglied der Europäischen Onkologiepflegegesellschaft (EONS) sowie Mitglied der Arbeitsgruppe Education EONS.

Yvonne Willems Cavalli kam in den 80er Jahren aus Holland ins Tessin und baute zuerst am Ospedale San Giovanni in Bellinzona die Onkologiepflege auf und förderte sie später während Jahrzehnten im ganzen Kanton Tessin. Zudem erlangte sie an der Universität von Surrey einen Master in Onkologiepflege. Nach langjähriger Mitarbeit in der Schweizerischen Interessengruppe Onkologiepflege, stand sie von 1998-2002 als erste Präsidentin dem ordentlichen Verein für Onkologiepflege vor. Mit dem Aufbau von Strukturen, dem Zugang zu Finanzen, sowie durch das Setzen von fachlichen Schwerpunkten sorgte Yvonne Willems Cavalli für Stabilität und Weiterentwicklung der Onkologiepflege in der Schweiz. Des Weiteren beteiligte sie sich als Co-Autorin an der Erstellung und Publikation von Standards für die Onkologiepflege.

Yvonne Willems Cavalli

Auch international engagierte sich Yvonne Willems Cavalli und förderte die Onkologiepflege beispielsweise als Präsidentin der Europäischen Fachgesellschaft (EONS) oder als Referentin an Kongressen. Beruflich leitet sie seit vielen Jahren als Pflegedirektorin den gesamten Pflegebereich der öffentlichen Spitäler im Kanton Tessin und ist Geschäftsleitungsmitglied der Gesamtorganisation, Ente Ospedaliero Cantonale, Bellinzona.

Lucienne Bigler-Perrotin engagiert sich seit Jahrzehnten als diplomierte Pflegefachperson in Onkologie und Palliativpflege und mit einem Master in «Führung von Systemen der Pflege und Gesundheit» (MA en gestion des systèmes de soins et de santé) für die Entwicklung der Onkologiepflege in der Romandie. Früher war sie als Pflegeexpertin am Universitätsspital Genf tätig, heute als Direktorin der Krebsliga Genf sowie als Vorstandsmitglied der Krebsliga Schweiz. Lucienne Bigler-Perrotin arbeitete bereits in

Lucienne Bigler-Perrotin

frühen Jahren in der Interessengruppe Onkologiepflege mit und war ab 2002 während 11 Jahren Vorstandsmitglied der Onkologiepflege Schweiz, einige davon als Vizepräsidentin.

Lucienne Bigler-Perrotin prägte mit ihrem unermüdlichen und fachkompetenten Engagement wesentliche Schwerpunkte und Angebote der Onkologiepflege Schweiz, wie beispielsweise:

- Aufbau und Leitung der Interessengruppe Genf
- Durchführung von Fortbildungen in der Suisse Romande
- Co-Autorin von verschiedenen Standards/Leitfaden für die Praxis und Übersetzungen
- Chefredaktorin der Zeitschrift Onkologiepflege – Suisse Romande

Als besonders herausragend ist das Anliegen von Lucienne Bigler-Perrotin zu erwähnen, Patienten und ihre Angehörigen als Personen in ihrem aktuellen Erleben und ihrer Umgebung wahrzunehmen. Ihnen als Menschen mit individuellen Bedürfnissen zu begegnen und Pflege mit ihrer spezifischen und ganzheitlichen Sichtweise anzubieten, dafür setzt sie sich mit Herzblut ein und hat damit beispielsweise auch das Berufsbild Onkologiepflege geprägt.

Der Vorstand OPS gratuliert den Ehrenmitgliedern für ihre ausserordentlichen Verdienste sehr herzlich und dankt ihnen für die jahrelange freundschaftliche Verbundenheit!

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Geschichte der Onkologiepflege in der Schweiz

Auf Initiative von Rosette Poletti, Françoise Maillard Strüby und Lise Plojoux aus Genf trafen sich ab 1979 Pflegefachpersonen, vorwiegend aus Bern, Lausanne, Genf, Luzern, Zürich, Basel und St. Gallen zum Austausch von Erfahrungen und Wissen.

1987 **Gründung der Schweizerischen Interessengruppe Onkologiepflege** beim Schweizerischen Berufsverband SBK. Präsidentinnen waren Agnes Glaus, Françoise Maillard Strüby und Yvonne Willems. Nebst den bereits erwähnten Personen gehörten zu den Pionieren dieser Zeit auch Anne Murphy, Bernarda Staffelbach, Gertrud Roth, Hansruedi Stoll, Josi Kiser, Annekäthy Bischoff, Brenda Schmid, Doris Bittel-Passeraub, Yolanda de Jong, Sistiana Regazzoni und Irène Bachmann-Mettler. Schwerpunkte dieser Jahre waren die Durchführung von Kongressen, Mitarbeit bei ersten Studien der SAKK, Wissens- und Erfahrungsaustausch.

1998 Gründung der Schweizerischen Vereinigung für Onkologiepflege (SVO/SBK) mit eigener Rechtspersönlichkeit unter der Präsidentin Yvonne Willems Cavalli.

Es wurden Vereinsstrukturen aufgebaut. Regionale Interessengruppen und Newsletters entstanden und man traf sich an internationalen und nationalen Kongressen. Themen wie Fatigue, verändertes Aussehen, Orale Mukositis wurden aktuell, untersucht und publiziert, Broschüren für Patientinnen und Patienten entwickelt und Standards definiert.

2002 Gründung der Onkologiepflege Schweiz (OPS) als eigenständiger Verein mit einer Geschäftsstelle. Übergabe der Geschäfte an Präsidentin Irène Bachmann-Mettler, Wahl von Vorstandsmitgliedern, wie Evelyn Rieder, Anita Margulies, Ursula Biederbost, Brenda Schmid, Lucienne Bigler-Perrotin, Mariuccia Schönholzer und Daniela Zahnd. Im Vordergrund stand die Weiterentwicklung von Vereinsstrukturen, Publikation von Standards, Fachwissen, Kongressen und insbesondere Fortbildungsangebote.

In der Praxis konnten Programme und Angebote – mit massgebender Initiative, Fachwissen und Mitarbeit von Onkologiepflegenden – aufgebaut werden.
Beispiele:
- Angebote in Palliative Care spitalintern und wohnortsnah
- Hospizdienste
- Breast Care Nurses-Programme
- *Look good feel better* Kurse
- Lernen mit Krebs zu leben
- Rehabilitationsprogramme und Survivorship-Angebote
- Nationale Strategie gegen Krebs
- Pflegeforschung in der Onkologie, wissenschaftliche Publikationen
- HöFa 1 und Nachdiplomstudium in Onkologiepflege
- Weiterbildungen auf akademischer Ebene
- Pflegeexpertinnen mit einem Master oder MAS Onkologiepflege arbeiten in der Onkologiepflege und bauen Programme auf.

Entwicklung Fachverband
Die Onkologiepflege Schweiz mit ihren fachlichen und regionalen Interessengruppen hat sich seit 2002 ebenso weiterentwickelt.
Beispiele:
- Pflegende der Pädiatrie gründeten eine Interessegruppe und führen Basiskurse und Tagungen durch.
- Über 30 Fortbildungen pro Jahr werden von der Gruppe Fortbildungen unter der Leitung von Anita Margulies aufgebaut.
- Jour Romandie und eine Tagung der Gruppe Gioti im Tessin werden durchgeführt.
- Das Berufsbild Onkologiepflegende wurde erarbeitet.
- Die Fachzeitschrift, aufgebaut von Evelyn Rieder, erscheint 4-mal jährlich.
- Einführungskurse und Netzwerke werden angeboten.
- Multiprofessionelle Arbeitsgruppe «Adhärenz bei oraler Tumortherapie»
- Erstellung von verschiedensten Praxis-Leitfäden und Leitlinien mit Experten und Expertinnen
- Mitarbeit in anderen Organisationen (Krebsliga Schweiz, Palliative CH, Plattform Palliative Care, Oda-Sante)
- Erarbeitung von Qualitätskriterien für die Praxis

Über 1200 Mitglieder der OPS engagieren sich heute auf unterschiedliche Weise in Praxis, Lehre und Forschung und sind zu einer Community zusammengewachsen, in der sich viele Mitglieder wohlfühlen, wo Gleichgesinnte sich finden, persönlich entwickeln, weiterbilden und fachlich austauschen können.

Die Onkologiepflege Schweiz dankt allen Mitgliedern und Verbündeten für ihre Energie, Inspiration und ihren täglichen Einsatz als Onkologiepflegende und für die Unterstützung der Onkologiepflege Schweiz.

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	26. – 27.09. + 07.11.2018	Olten	**Einführungskurs für Pflegende in das Fachgebiet Onkologie**
10	04.10.2018	Zürich	**Lungentumoren** Neue Ansätze in der Therapie
	11.10.2018	Olten	**Cancer Survivorship** Neue Ansätze in der Therapie
	25.10.2018	Zürich	**Hals-Nasen-Ohren Tumoren / Einführung in die Radiotherapie** Diagnostik und Behandlung. Radiotherapie mit Schwerpunkt HNO Tumoren.
	31.10.2018	Olten	**Netzwerk Onkologiepflege in der Spitex**
11	01.11.2018	Zürich	**Hämatologische Tumoren II** Akut oder chronisch – die Leukämien
	07.11.2018	Zürich	**Netzwerk für Führungspersonen Onkologiepflege**
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	15.11.2018	Zürich	**Hauttumoren / Maligne Wunden** Diagnostik und Behandlung
	22.11.2018	Zürich	**Führungsseminar** **Kommunizieren in anspruchsvollen Situationen**
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healthbook: Keep Up-To-Date With the Latest Developments and Insights in Oncology and Hematology

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healthbook is an independent online medical journal and exchange platform for evidence-based medical information. By offering a faculty-recommended journal watch, among other features, healthbook aims to meet the needs of Swiss physicians providing regular updates on the latest, evidence-based clinical data across many areas of medicine, which are accessible through registration. This supports our 'Swiss doctors for Swiss doctors' approach. With this, healthbook enables physicians and healthcare professionals to keep up-to-date with the latest developments and insights in their fields of interest.

Introduction

healthbook went live in June 2016 and follows a 'Swiss physicians for Swiss physicians' approach.[1] It covers several disease areas, including Oncology · Hematology – the largest and most frequently accessed disease area on healthbook. The latest scientific articles, news from conferences, publications, hot topics, case reports, expert opinions, CME-accredited e-learning modules, patient cases and videos are posted regularly.

healthbook also reports from international conferences, providing summaries and expert opinions in **healthbook Congress Highlights**. This is a new print and online Swiss medical journal. Recently healthbook ASCO Highlights and healthbook EHA Highlights and earlier this year healthbook ASH Highlights and healthbook ELCC Highlights were successfully released.

More recently, healthbook launched **healthbook NET**.[1] This social media platform has been developed with physicians in mind to allow them to **share their own publications and patient cases** with colleagues and experts in a safe environment.

On healthbook, oncologists and hematologists can also find slides and video recordings from the annual **Swiss Summit on Hemato-Oncology** (SSHO®), which is jointly organized by Mediscience GmbH and H+O communications Ltd. SSHO® is a half-day CME-accredited event that takes place simultaneously in more than 10 centers across Switzerland via videoconference. Next year the SSHO will take place on 4 April 2019 and will be celebrating its 10-year anniversary.

healthbook: An Independent Online Medical Journal

healthbook is an online medical journal that has been successfully introduced to physicians and other healthcare professionals. In July 2018 alone, healthbook attracted 5,396 active visitors and a total of 104,882 page views. In terms of page views, Oncology · Hematology is the most accessed disease area on healthbook. Approximately one-third of all page views (35,417 of 104,882) were attributed to this disease area (**Figure 1**).

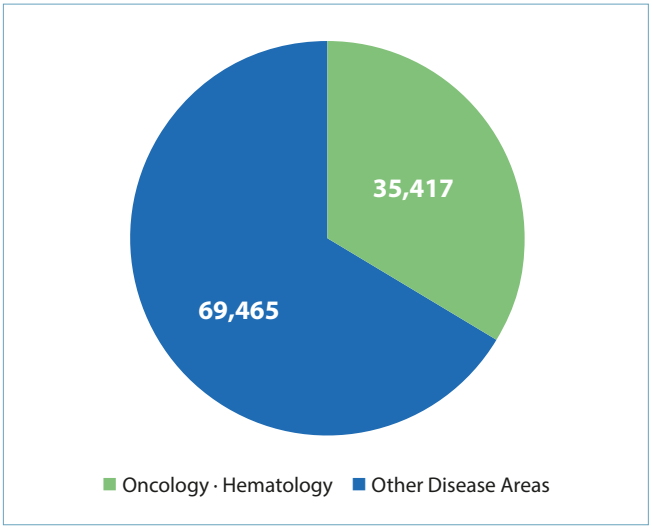

Figure 1. Number of page views on healthbook

healthbook also has a very loyal user base. More than two thirds of the active users (69%) visited healthbook at least twice in July 2018. The remaining 31% were new visitors (**Figure 2**). On average, each active user visited 19 pages in one month.

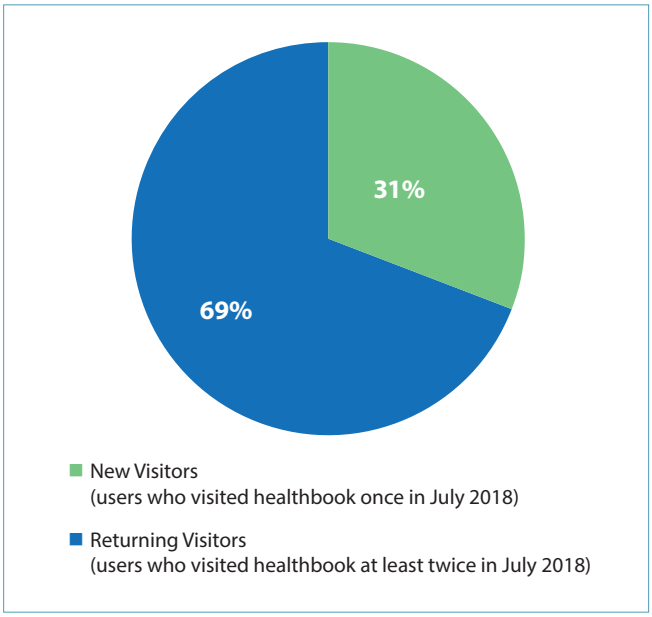

Figure 2. User loyalty on healthbook.ch

To attract more visitors accessing healthbook via mobile phone (responsive web design already exists), healthbook is currently undergoing a redesign that will be released along with new healthbook tools in the coming weeks. These will allow users to search for, among other things, possible drug–drug interactions or the prescribing information of drugs.

healthbook and the SSHO®: Stay Informed on What's New in Hematology

The SSHO® is an annual CME-accredited event for hematologists and oncologists as well as any interested physicians who want to stay informed about the newest developments in hematology. Invited experts discuss the current state of the art and future directions of diagnosing and treating patients with hematological malignancies. Topics at this year's SSHO®, which was held on 19 April, included chronic lymphocytic leukemia, multiple myeloma, mantle cell lymphoma, chronic myeloid leukemia and rare indolent lymphoma. Video recordings and slides from this conference can be accessed for free on healthbook. Registration is required for new users, which gives access to all of healthbook's content.[1]

The SSHO® Concept

Each year, the SSHO® is organized by Mediscience GmbH and H+O communications Ltd. under the auspices of the SAKK with healthbook being the media partner. It is hosted by a main center (**Figure 3**). The main center, which rotates each year, is connected via a live webcast to several satellite centers. This allows hematologists and oncologists to attend the SSHO® at a local center, often at the same hospital at which they are practicing. In addition, a live webcast is offered on healthbook for those who cannot attend the SSHO® at one of the centers (**Figure 3**). This concept of bringing continuing medical education to physicians, having one main center, several satellite centers and a live webcast has been well received. Earlier this year, 215 participants signed up for the 9th SSHO® 2018.

Figure 3. The SSHO® concept allows participants to attend this annual meeting at a local center

10 Years SSHO®

Next year on 4 April 2019, the SSHO® will celebrate its 10th anniversary (**Figure 4**). The planning of the 10th SSHO® 2019 is already under way. It will be hosted by the main chairs Prof. Dr Thomas Pabst and Prof. Dr Sacha Zeeleder at the Inselspital, Bern, and a total of 11 satellite centers have already confirmed their participation.

Topics that will be presented include Hodgkin lymphoma in young and older patients; when to stop (or not to stop) treatment in patients with chronic myeloid leukemia; is R-CHOP still the preferred treatment option for all patients with aggressive lymphoma or diffuse large B cell lymphoma; and the use of liquid biopsies and CAR T-cell therapies in clinical practice (**Figure 4**).

healthbook Congress Highlights

The healthbook team regularly attends and reports from international congresses such as ASCO® and EHA®. Recently, healthbook published two journals – healthbook ASCO Highlights with an editorial by Prof. Daniel Betticher and healthbook EHA Highlights with an editorial by Dr Dr Davide Rossi. These publications summarize the latest clinical trial data presented at ASCO and EHA. In addition, they provide opinions from Swiss experts on the latest developments in oncology and hematology research. Both journals can be conveniently downloaded from healthbook.ch.

Register on healthbook to download **healthbook ASCO Highlights** and **healthbook EHA Highlights**

Figure 4. On 4th April 2019 the SSHO® will celebrate its 10-year anniversary

healthbook NET: Learn From Peers and Colleagues by Discussing and Sharing Your Patient Cases and Publications

The latest feature launched by healthbook is healthbook NET.[1] This social medial platform, which can be accessed directly via www.healthbook.network, encourages physicians to discuss and share their own publications and patient cases with a network of colleagues and experts (**Figure 5**).

The patient cases section is only accessible to physicians; other healthcare professionals and representatives from pharmaceutical or medical device companies are not granted access. This makes the patient case section of healthbook NET a safe and protected environment for physicians to share and discuss their experiences in diagnosing and treating patients. Users already registered on healthbook.ch can use the same account to access healthbook NET.

Figure 5. On healthbook NET, physicians can share and discuss their own publications and patient cases

Key facts:

- healthbook is an independent Swiss online medical resource and online medical journal, which follows a 'Swiss physicians for Swiss physicians' approach.
- The SSHO® is an annual CME-accredited meeting aimed at conveying the current knowledge in hematology to interested physicians.
  - Interested oncologists and hematologists can attend the SSHO® for free either at the main center, one of the satellites or via the live webcast hosted on healthbook.
  - Following each SSHO®, all slides and video recordings are made available on healthbook.
  - Next year, SSHO® will celebrate its 10th anniversary.
- healthbook Congress Highlights provides oncologists and hematologists with the latest insights from international congresses as well as expert opinions.
- healthbook recently launched healthbook NET – a social media platform encouraging physicians to discuss and share their own publications and patient cases.

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1. Holm S., Belzar K., Reynolds T., Heitlinger E. healthbook – the Swiss Online Medical Resource and Discussion Platform for Your Cases and Publications. Schweizer Krebsbulletin. 2018;38(02):200–3.

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European Thoracic Oncology Platform

Heidi Roschitzki-Voser, ETOP Coordinating Office, Bern

Accrual Overview of Ongoing ETOP Trials (as of 6 August 2018).

	STIMULI		NICOLAS		PEARLS	PROMISE-meso	BOOSTER
	Enroled	Randomised	Enroled under protocol version		Randomised	Randomised	Randomised
			1.0	2.0 & 3.0			
Total accrual	**191**	**112**	**12**	**82**	**526**	**143**	**117**
Swiss Centres	12	8	4	12	37	26	4

Safety results from the ETOP 6-4 NICOLAS trial presented at the 2018 ASCO Annual Meeting

The feasibility of combined chemo-radiotherapy and concurrent PD-1 inhibition is of high scientific interest. Preclinical models have shown promising results but concurrent immune-checkpoint inhibition and radical thoracic radiotherapy has never been assessed in a clinical trial so far.

The phase II NICOLAS trial evaluated the safety terms of grade ≥3 pneumonitis of nivolumab when given concurrently to first-line chemo-radiotherapy in stage III NSCLC. The results from the early interim safety analysis of 21 patients were presented at the 2018 ASCO Annual meeting in Chicago. The data provided evidence that the addition of nivolumab concurrently to chemo-radiotherapy is safe and tolerable. Also in the extended safety cohort with 58 patients that received at least one dose of nivolumab treatment, no unexpected adverse event or increased risk was observed.

In a next step, the 1-year progression-free survival will be evaluated in the expansion cohort of 78 patients that received concurrent chemo-radiotherapy plus nivolumab treatment.

ETOP 12-17 ALERT-lung trial

This is an international, multicentre single arm phase II trial, evaluating the activity of alectinib in pre-treated patients with RET-rearranged advanced NSCLC with the primary objective to assess the efficacy of alectinib in terms of overall response. The trial will be conducted in Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Slovenia, Spain and Switzerland. The protocol was released in September 2017. All three participating Swiss sites and four sites in Spain are activated for the trial, with other sites following rapidly.

ETOP 13-18 BEAT-meso trial

This is a multicentre, randomised, open label, phase III trial comparing atezolizumab plus bevacizumab and standard chemotherapy versus bevacizumab and standard chemotherapy as first-line treatment for advanced malignant pleural mesothelioma.

Malignant pleural mesothelioma is a rare and aggressive cancer arising from the mesothelial surface of the pleura. The incidence in Europe is about 20 per million. Only in 10-15% of the patients the disease is resectable and systemic therapy is often the only treatment option for these patients. The currently approved first-line therapy is chemotherapy with cisplatin plus pemetrexed with a median overall survival of approximately 12 months.

Vascular endothelial growth factor is a key mitogen for malignant pleural mesothelioma cells and targeting angiogenesis has a clear rational in this disease. The addition of bevacizumab to cisplatin and pemetrexed has shown to

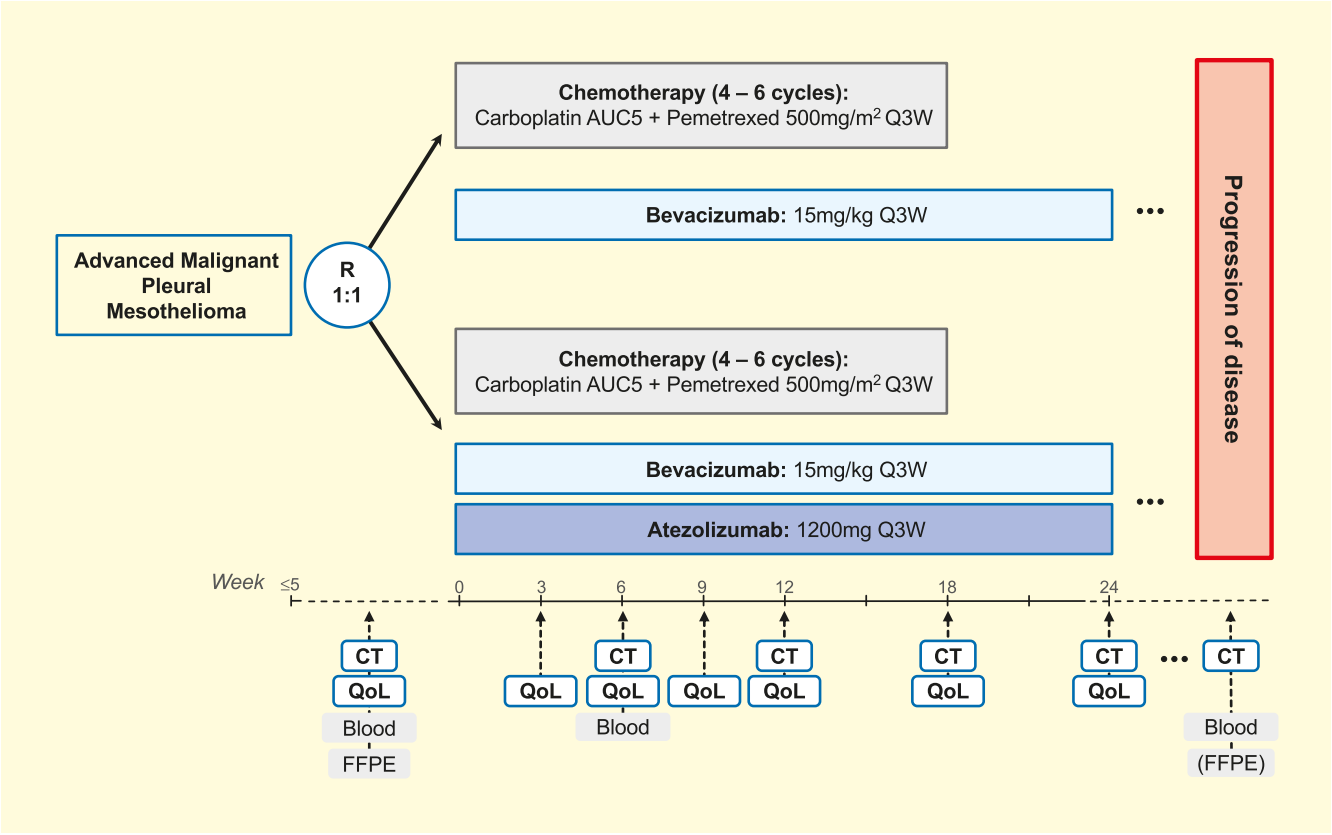
significantly improve overall survival in the randomised phase III MAPS trial. In addition, there is preclinical evidence for the efficacy of combining anti-angiogenic therapies with immunotherapy and clinical studies have already shown promising results.

The aim of the BEAT-meso trial is to address whether the addition of anti-PD-L1 treatment to standard chemotherapy and bevacizumab improves the outcome of treatment-naïve patients with advanced malignant pleural mesothelioma.

The trial will randomise a total of 320 patients during approximately three years, and will be conducted in Switzerland, Belgium, France, Italy, Portugal, Slovenia, Spain, and the United Kingdom. Atezolizumab and bevacizumab will be available for free through the trial; carboplatin and pemetrexed will have to be sourced locally.

The protocol will be released in August 2018, and we are looking forward to an active participation from all involved sites.

Trial Scheme of the ETOP 13-18 BEAT-meso trial



ETOP Residential Workshop and ETOP Annual Meeting 2018 in Barcelona

Registrations are now open for the 7th ETOP Residential Workshop and the ETOP Annual Meeting 2018 that will take place back-to-back in Barcelona, Spain, 7-10 November 2018. Further information can be found on the ETOP Website: www.etop-eu.org.

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Longer-term results from the SOFT and TEXT trials

Heidi Roschitzki-Voser, IBCSG Coordinating Center, Bern

Addition of ovarian suppression to adjuvant tamoxifen significantly improved disease-free and overall survival vs tamoxifen alone in premenopausal women with HR+ breast cancer after median follow-up of 8 years.

The results from pre-specified updated analyses of SOFT and the combined analysis of data from SOFT and TEXT after a median follow-up of 8 and 9 years, respectively, were presented at the 2017 San Antonio Breast Cancer Symposium by Gini Fleming and Prue Francis and published in The New England Journal of Medicine [1].

In the trials, premenopausal women with hormone receptor (HR)-positive breast cancer were randomized to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression in SOFT, and to tamoxifen plus ovarian suppression or exemestane plus ovarian suppression in TEXT. Randomization was stratified by receipt of chemotherapy.

The 8-year disease-free survival rates in SOFT were 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with exemestane plus ovarian suppression (for tamoxifen plus ovarian suppression versus tamoxifen alone: hazard ratio [HR] = 0.76, P = 0.009; for exemestane plus ovarian suppression vs tamoxifen alone: HR = 0.65, 95% confidence interval [CI] = 0.53–0.81). Overall survival at 8 years was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus ovarian suppression (HR = 0.67, P = 0.01, versus tamoxifen alone), and 92.1% with exemestane plus ovarian suppression (HR = 0.85, 95% CI = 0.62–1.15, versus tamoxifen alone); the respective survival rates among women who remained premenopausal after chemotherapy were 85.1%, 89.4%, and 87.2%.

In the combined analysis of the two trials including patients who were assigned to receive ovarian suppression, 8-year disease-free survival rates were 86.8% with exemestane plus ovarian suppression versus 82.8% with tamoxifen plus ovarian suppression (HR = 0.77, P <0.001) and 8-year overall survival rates were 93.4% versus 93.3% (HR = 0.98, P = 0.84). The majority of patients in the two trials had HER2-negative disease. Among these women who received chemotherapy, the 8-year rate of distant recurrence with exemestane plus ovarian suppression was lower than the rate with tamoxifen plus ovarian suppression by an absolute 7.0% in SOFT and 5.0% in TEXT. Adverse events of grade ≥3 occurred in 24.6% of the tamoxifen group, 31.0% of the tamoxifen plus ovarian suppression group, and 32.3% of the exemestane plus ovarian suppression group. The authors concluded that, among premenopausal women with HR-positive early breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher rates of both disease-free and overall survival than tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group. Follow-up of the SOFT and TEXT trials continues.

At the 2018 ASCO Annual Meeting, Meredith Regan presented a further analysis of the SOFT and TEXT results. Her presentation focused on patients with HR-positive, HER2-negative disease and detailed the absolute improvements in freedom from distant recurrence that might be achieved across the spectrum, from very high risk of recurrence to a low risk of recurrence, utilizing treatment with exemestane plus ovarian suppression, or tamoxifen plus ovarian suppression versus tamoxifen alone [2].

ASCO poster discussion of SOLE results on molecular alterations and late recurrence

Women with hormone receptor-positive early breast cancer have a persisting risk of relapse even after 4–6 years of adjuvant endocrine therapy and the question is whether there are any biomarkers to predict late recurrence and thereby improve the clinical management of these patients. From the 4884 postmenopausal women enrolled in the extended adjuvant intermittent letrozole versus continuous letrozole (SOLE) trial, 3162 had tumor samples of the primary breast cancer available and were eligible for the molecular analyses.

A molecular analysis of the primary breast cancer from postmenopausal women enrolled in the SOLE trial was performed to identify prognostic factors and potential molecular targets. The associations of genomic alterations with breast cancer free-interval and distant recurrence free-interval were assessed. With this analysis it could be shown that patients with hormone receptor-positive node-positive

1. Francis PA, et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med 379: 122-137, 2018.
2. J Clin Oncol 36, 2018 (suppl; abstr. 503).

The SOFT Team at ASCO 2018. From left to right: Prue Francis, Meredith Regan, Gini Fleming.

breast cancer with copy number gain for *FGFR1* had an increased risk of late recurrence despite extended therapy. *FGFR1* analysis may improve the risk stratification in this population and represent a potential therapeutic target.

A poster with these results was presented by Elena Guerini Rocco et al. at ASCO 2018 and discussed by Erica L. Mayer, during the poster discussion session [3].

Two ASCO poster presentations for POSITIVE

IBCSG 48-14 / BIG 8-13 POSITIVE is a prospective, single arm, international trial to assess if temporarily interrupting adjuvant endocrine therapy (for up to 2 years) for young women with endocrine responsive breast cancer who desire pregnancy is safe in terms of risk of breast cancer recurrence. Sample size is 500 evaluable patients and as of 30 April 2018, 234 patients have already been enrolled.

A trial in progress poster was presented by Ann Partridge et al. at the ASCO Annual Meeting in Chicago this June. The poster generated a lot of interest and we hope that this will further help to recruit patients in this very important trial.

Another poster for the POSITIVE trial presented by Zhuoxin Sun et al. at this ASCO Meeting, described the estimation of a historical control rate for single arm trials. POSITIVE is a single arm trial and in order to better estimate the historical control rate, methods were developed and applied using the data from the SOFT/TEXT phase III trials.

A cohort of 1499 SOFT and TEXT patients where identified that met the POSITIVE eligibility criteria, including having received 18 to 30 months of endocrine therapy. Two approaches were used and compared: Method I included all eligible patients and calculated the annualized hazard rate of breast cancer free interval (BCFI) events directly over the first 3 years and the 3-year BCFI failure rate, based on Kaplan-Meier estimates. Method II was a more refined approach taking into account the potential selection of eligible patients who would enrol in POSITIVE by group-matching the patient characteristics of SOFT/TEXT patients to the first 149 POSITIVE patients that were enrolled until 1 October 2017.

These methods will aid in the interpretation of the final analysis of POSITIVE. In order to assure a consistent and robust estimate of a historical control rate across different cohorts, a next step is to apply the methods using data also from other sources [4].

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3. J Clin Oncol 36, 2018 (suppl; abstr. 517).
4. J Clin Oncol 36, 2018 (suppl; abstr. 552).

IELSG Clinical Trials Status

Emanuele Zucca, International Extranodal Lymphoma Study Group, Bellinzona, Switzerland

Here we provide a brief summary and the current status of the prospective international clinical trials.

Open Studies

IELSG37 – A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy after rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL). The IELSG37 is a phase III multicenter study aiming to evaluate the role of involved field radiotherapy in patients with primary mediastinal large B-cell lymphoma that achieve a negative PET-scan following standard chemoimmunotherapy treatment. Thus far, 441 (out of 540) patients have been recruited in 69 different institutions in 12 countries (Italy: 314, UK: 37, Ukraine: 25, Switzerland: 15, Canada: 9, Poland: 11, Norway: 10, Sweden: 6, Germany: 4, Czech Republic: 4, Portugal: 3, USA: 3). 383 have completed R-chemotherapy and underwent central PET review, 193 with negative PET scan have been randomized between radiotherapy or observation.

IELSG40 - A phase II trial addressing feasibility and activity of clarithromycin + lenalidomide combination: a full oral treatment for patients with relapsed/refractory extranodal marginal zone lymphoma (CLEO Trial). This study on MALT lymphoma is open for recruitment in Italy, Austria and Spain. Twenty-three patients have already been included.

IELSG42 – An international phase II trial assessing tolerability and efficacy of sequential Methotrexate-Aracytin-based combination and R-ICE combination, followed by high-dose chemotherapy supported by autologous stem cell transplant, in patients with systemic B-cell lymphoma with central nervous system involvement at diagnosis or relapse (MARIETTA regimen). The accrual for this study will be soon completed. Indeed, 74 patients (52 in Italy, 18 in UK, 4 in The Netherland and 1 in Switzerland) have been already included. In Switzerland, the MARIETTA protocol is approved and open in three centers: IOSI Bellinzona, Inselspital Bern and Universitätspital Zürich.

IELSG43 – High-dose chemotherapy and autologous stem cell transplant or consolidating conventional chemotherapy in primary CNS lymphoma - randomized phase III trial (MATRix). This study is the follow-on study of the IELSG32 study. Thus far, 239 have been included: 191 in Germany, 14 in Italy and 2 in Denmark. Recently, an amendment aiming to increase the sample size (from 250 to 330 patients) has been approved in Germany. As required by the Sponsor (City of Stuttgart), the other participating countries submitted the amendment to their Ethic Committee and Health Authorities only after the German approval. The new version of the protocol also answers all questions addressed by Swiss EC and Swissmedic. As soon as the local Ethic Committees and Swissmedic approve the new version, the centers of Kantonsspital Aarau, IOSI Bellinzona, Inselspital Bern, Centre Pluridisciplinaire d'Oncologie Lausanne, Kantonsspital Luzern and UniversitätsSpital Zürich will be opened and able to include patients.

The IELSG37, IELSG42 and IELSG43 studies are conducted in Switzerland in cooperation with the Swiss Group for Clinical Cancer Research (SAKK).

Future Studies

IELSG45 – Randomized phase II trial on fitness- and comorbidity- tailored treatment in elderly patients with newly diagnosed primary CNS lymphoma (FIORELLA Trial). The objective of Part A of this trial is to compare the efficacy of a new maintenance treatment consisting of oral lenalidomide with the oral procarbazine maintenance currently in use, in elderly (≥70 years) patients with newly diagnosed PCNSL eligible to receive HD-MTX-based induction chemo-immunotherapy. For Part B, the aim is to evaluate the efficacy of concomitant

chemo-immuno-radiotherapy administered as induction treatment, followed by temozolomide maintenance in elderly (≥70 years) patients with newly diagnosed PCNSL not eligible to receive the induction treatment of Part A. The study has been recently submitted in Belgium, Denmark, Finland, Italy and Switzerland. Israel is also planning to join this study.
Five Swiss centers will activate the IELSG45 protocol: Univesitätsspital Basel, Inselspital Bern, CHUV Lausanne, Kantonsspital St. Gallen and IOSI Bellinzona. The study will be conducted in cooperation with the Swiss Group for Clinical Cancer Research (SAKK).

IELSG47 – Phase II study of combination ibrutinib and rituximab in untreated marginal zone lymphomas (MALIBU Trial). Aim of this study is to assess the safety and efficacy of the combination of rituximab and ibrutinib in EMZL patients and to explore its activity in SMZL and NMZL. Centers from Belgium, France, Italy, United Kingdom, Portugal and Switzerland already showed interest in this study the activation of which is planned in the first quarter of 2019.

Closed Studies

IELSG36 – Bendamustine and Rituximab for the treatment of Splenic Marginal Zone Lymphoma (BRISMA). Objective of the IELSG36 study is to evaluate the efficacy and the safety of R-Bendamustine in symptomatic Splenic Marginal Zone Lymphoma patients. A poster presentation at ASH 2017 displayed the first analysis results and the final manuscript will be submitted soon.

IELSG38 – A phase II study of Chlorambucil in combination with subcutaneous rituximab followed by maintenance therapy with subcutaneous rituximab in patients with extranodal marginal zone B-cell lymphoma of Mucosa Associated Lymphoid Tissue (MALT lymphoma). The IELSG38 study will be the first study to evaluate a maintenance treatment with subcutaneous rituximab in these patients with extranodal MALT B-cell lymphoma. Accrual has been completed in 2016 and the first results have been presented in a poster at ASH 2017.

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SAVE THE DATE

The next IELSG Annual Meeting will be held in Paris (France) on April 12-13, 2019

To register of for further information: *www.ielsg.org*
Or contact *ielsg@eoc.ch*

LYFE – LYMPHOMA FORUM OF EXCELLENCE

“What’s new in lymphoid neoplasias?”

The LyFE course is accredited by the European Accreditation Council for Continuing Medical Education (EACCME)

The next LyFE course will take place in Bellinzona on February 8-10, 2019, starting mid-morning of Friday 8th.

Registration costs, accommodation, lunches and coffee breaks are covered.

Participants will have to cover only the travelling expenses and dinners.

For participants outside Switzerland, grants are available for the travelling expenses.

Since 2004, the Oncology Institute of Southern Switzerland (Istituto Oncologico della Svizzera Italiana, IOSI) has organized a yearly course in which the latest knowledge in lymphoid neoplasias, including myelomas, is summarized. A particular feature of the course is that the program is based on discussions of cases: these will be the starting point for most lectures, which will mainly give an update on each specific topic.

Accepted participants: *on a first-come/first-served basis*

For further information and registration (deadline: **30th November 2018)**, you may contact:

LyFE Secretariat
Ospedale San Giovanni
6500 Bellinzona, Switzerland
Tel. +41 (0)91 811 86 66
info@lymphomaforum.ch
www.lymphomaforum.ch

The course is supported by Educational Grants.

Very rare side effects of rituximab?

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Key words: Marginal zone lymphoma, rituximab, aseptic meningitis

Abstract
We present a case of a 53-year-old female with splenic marginal zone lymphoma and a diagnosis of uveitis and aseptic meningitis during treatment with rituximab. Having ruled out other possible causes of aseptic meningitis, we concluded that the most likely diagnosis was that of drug induced aseptic meningitis (DIAM), related to the rituximab therapy. Steroid treatment resulted in a complete symptoms resolution.

Introduction
Rituximab is anti-CD20 monoclonal antibody approved for the treatment of non Hodgkin lymphomas, rheumatoid arthritis and refractory autoimmune cytopenia, [1-4]. The safety profile of rituximab is good with the most frequent side effects being infusion-related reactions and hypogammaglobulinemia; neurological symptoms such as paraesthesia, insomnia and peripheral neuropathy are very rare [5]. Here we report a case of aseptic meningitis developed in a patient with splenic marginal zone lymphoma (SMZL) following treatment with rituximab.

Case report
A 53-year-old female with no remarkable medical history was referred to our department in May 2017 due to the persistence of asthenia, drenching night sweats, dyspepsia and early satiety. She presented with abnormal blood counts: haemoglobin, 116 g/L; leucocytes, 143.0x109/L (lymphocytes, 96.5%), platelets, 125x109/L and an increased LDH (1273 U/L; upper limit normal: 500 U/L). Renal and liver functions tests were normal.

A positron emission tomography-computed tomography (PET/CT) scan showed a massive splenomegaly (23x7x16 cm) without lymphadenopathies. A bone marrow biopsy revealed diffuse infiltration of B-cell lymphoma with low grade histological features (BCL2, CD20, CD79a positive, Cyclin D1, SOX11, CD5, CD10, CD23, BCL6 negative), MYD88 (L265P) was not mutated. A FISH (fluorescence in situ hybridization) analysis showed chromosome 17 (TP53) and 13q rearrangements. The patient was therefore diagnosed with stage IVBs SMZL.

First line treatment with rituximab (375 mg/m^2) as monotherapy for 4 weekly doses was started in June 2017 and the patient achieved a complete metabolic remission at PET/CT scan (Deauville score 1) and reduction of splenic diameter (15 cm versus 23 cm before treatment start). A bone marrow biopsy showed a complete disappearance of the lymphoproliferative infiltrate while FISH analysis was negative. Consolidation therapy with 4 additional weekly rituximab administrations was given between September and November 2017.

Despite an excellent response to treatment, during rituximab consolidation, the patient presented fatigue, recurrent headaches, poly-arthralgia and myalgia. A transient skin eruption was also described by the patient, together with recurrent (low grade) night fever. The patient also referred transient vestibular symptoms associated with hearing loss.

Therefore, we performed a brain magnetic resonance imaging (MRI) which did not provide a clear explanation for these symptoms, but led to the incidental diagnosis of a left temporal meningioma of 1 cm of diameter which, however, could not explain the symptoms. To rule out a paraneoplastic syndrome, a new PET/CT scan was performed in January 2018 which confirmed the lymphoma remission.

Subsequently, the patient also developed a left conjunctival erythema associated with visual loss. An ophthalmology consultation led to the diagnosis of left uveitis without any clear cause. All the infective screening was negative, and to exclude an autoimmune disease, diagnostic tests were performed: angiotensin-converting enzyme (ACE) and human leukocyte antigen (HLA) B27 tests were negative while HLA B51 test was positive.

A lumbar puncture was performed and showed pleocytosis (157.3 Lc/µL, normal value <5.0 Lc/µL), an increase of proteins (1617 mg/L, normal range 200-400 mg/L) and normal

glucose level without evidence of lymphoma involvement. An infectious cause was excluded on microbiological examination. The possibility of an immune-related meningitis was taken into consideration; however, systemic lupus erythematosus (SLE) was excluded because most clinical and laboratory (autoimmune antibodies such as ANA, ANCA and Anti nucleus were only slightly out of range) criteria for its diagnosis were absent. A conclusive diagnosis of Behçet's syndrome was also not possible, despite HLA B51 positivity, due to the absence of the typical clinical manifestations and the absence of other diagnostic criteria.

Therefore, our final diagnosis was that of drug induced aseptic meningitis (DIAM) possibly triggered by treatment with rituximab. A chronological correlation of symptoms appearance and symptoms exacerbation with rituximab infusions further supported this correlation. Accordingly, this case was reported to the Swiss authority responsible for the authorization and supervision of therapeutic products (Swissmedic).

The patient, in February 2018, started steroid therapy (Prednison 100 mg/day), which resulted in rapid symptoms improvement. However, uveitis persisted and required a left vitrectomy for diagnostic purposes which indeed excluded lymphoma involvement.

After 4 months of steroid therapy, a lumbar puncture was repeated and showed a reduction of pleocytosis (20.8 Lc/µL vs 157.3 Lc/µL at diagnosis), with normal proteins and glucose levels. Brain MRI was also repeated and showed the known meningioma unchanged in size. A MRI of the spine, however, showed a leptomeningeal enhancement predominant in the cauda equina consistent with an autoimmune poliradiculopathy (in differential diagnosis an arachnoiditis post lumbar puncture; a leptomeningeal carcinomatosis or a primary lymphoma involvement deemed less probable). The patient is currently completely asymptomatic on a low dose of steroids (7.5 mg/day of prednison) with the plan to slowly further reduce up to complete withhold of steroids in the next weeks.

Discussion

The introduction of the anti-CD20 monoclonal antibody rituximab in the standard of care, improved outcomes for most patients with non-Hodgkin lymphoma [1, 2]. The most frequent side effects associated with rituximab consist in infusion-related reactions, hypogammaglobulinemia and neutropenia, rash, nausea, hypotension, infections (such as herpes zoster, local candidiasis, reactivation of hepatitis B virus infection) and bronchitis [5, 6].

Neurological adverse events are very uncommon, however, there are some reports of progressive multifocal leukoencephalopathy (PML) associated with rituximab and caused by reactivation of a latent JC polyoma virus, while other neurological side effects like peripheral neuropathy, convulsions, fatal ischemic and hemorrhagic stroke have been rarely described [5-7].

Here we present a case of aseptic meningitis in a patient with SMZL treated with rituximab monotherapy. Causes of aseptic meningitis include: autoimmune disease such as sarcoidosis, SLE, rheumatoid arthritis, Behçet's syndrome, Vogt-Koyanagi-Harada syndrome, malignancy (leukaemia, lymphoma, metastatic carcinomas and adenocarcinomas) and drugs [8-10].

Histologic exam of the vitrectomy specimen and cytologic evaluation of the CSF did not detect evidence of lymphoma, and CNS involvement in marginal zone lymphoma is extremely rare.

Drug-induced aseptic meningitis (DIAM) is a rare adverse event of numerous agents [10, 11]. The clinical presentation is the same of meningitis from other causes. CSF findings are characterized by pleocytosis, elevated protein level, and normal glucose level, with negative microbiological investigations (culture and PCR based investigation). Therefore, apart from a chronological relationship, there are no clinical or biological parameters that can confirm this diagnosis; the rechallenge with the suspected drug could be the only confirmatory test for DIAM but considering its correlated risks, usually it is not performed and the diagnosis of DIAM remains only an exclusion diagnosis [12, 13].

Drugs frequently associated with aseptic meningitis are non steroidal anti-inflammatory drugs (NSAIDs), antimicrobics (trimethoprim-sulfamethoxazole), intravenous immunoglobulins, monoclonal antibodies (cetuximab, ipilimumab, infliximab, nivolumab, pembrolizumab), anticonvulsivants (lamotrigine, carbamazepine), vaccines (MMR) and miscellaneous (allopurinol, azathioprine, cytarabine, salazopyrine and methotrexate) [11, 14].

The most frequent DIAMs are related to use of NSAIDs, especially Ibuprofen, in patients affected by SLE [15], Sjogren Syndrome [16], and mixed connective tissue disease [17]. More recently, the incidence of neurologic immune-related adverse events (irAEs) due to the administration of immune checkpoint inhibitors (ipilimumab, nivolumab and pembrolizumab) is in some series about 1% and include Guillain-Barre syndrome (GBS), myasthenia gravis, myopathy, aseptic meningitis and chronic inflammatory demyelinating polyneuropathy [18].

The possible mechanisms that induce DIAMs are divided into 2 main categories. The first is a direct chemical «irritation» of the meninges due to the intrathecal administration of the drug; the second mechanism is an immuno-

logical hypersensitivity reaction (type I to IV). The type I and II hypersensitivity are not usually observed in the settings of DIAMs. Type III (immune complex-mediated reaction) is a plausible mechanism of DIAMs in patients affected by SLE. The type IV reaction (T cell-mediated hypersensitivity) is probably associated with DIAMs secondary to administration of monoclonal antibodies [10].

Management of DIAM consists of discontinuing the suspected medication, treatment with IV antibiotics until bacterial meningitis has been ruled out and supportive care. Most meningeal signs and symptoms improved within 24 to 48 hours after withdrawal of the drug. In DIAMs related to monoclonal antibodies, a systemic steroid therapy is recommended and in patients with meningo-radiculo nevritis a clinical improvement could request at least 4 months from the start of steroid therapy and CSF normalization after about 3 weeks [11].

The prognosis is excellent with complete resolution of symptoms and usually no evidence of neurologic sequelae. In the case here reported a patient with initial diagnosis of splenic marginal zone lymphoma (SMZL) in complete remission after treatment with Rituximab alone for a total of 8 administrations developed an aseptic meningitis likely rituximab-related. This suspect was founded on a strong chronological relationship between the onset of neurological symptoms and the administration of immunotherapy.
To the best of our knowledge, this is the first report of a likely rituximab-associated aseptic meningitis in the literature. This case was reported to Swissmedic, the authority for pharmacovigilance.
In Switzerland, so far, there has been no other cases of rituximab-related aseptic meningitis but in WHO pharmacovigilance registry (*https://www.who-umc.org/vigibase/vigibase/*), there are 19 cases of uveitis and 16 cases of meningitis in patients treated with only rituximab (total of 55.734 cases about rituximab side effects).

In conclusion, our case describes a very rare adverse event of rituximab treatment, a drug induced aseptic meningitis. This diagnosis is very difficult and should be considered when other causes are ruled out and there is a chronological criteria with the use of a specific drug.

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