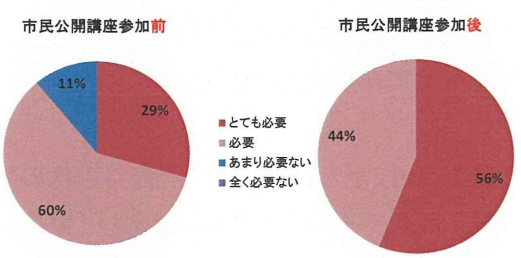
年代（121名）は、10代5名（1.7%）、20代5名（1.7%）、30代36名（29.8%）、40代29名(24.0%)、50代21名(17.4%)、60代以上25名（20.7%）であった。
がん経験（116名）については、「自分が患者である」14名（12.3%）、「家族が患者である」44名（38.0%）、自分も家族も患者である1名（0.86%）、どちらでもない57名（49%）であった。
職種別（106名）では、医療関係者44名（41.5%）、主婦32名（30.2%）、会社員2名(1.9%)、保健・福祉関係者10名(9.4%)、教育関係者7名（6.6%）であった。

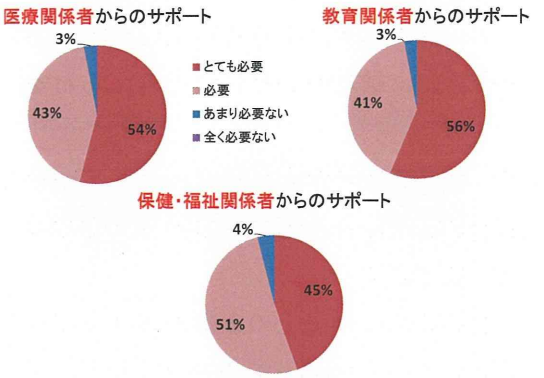
（1）子どもに話す必要性について、市民公開講座前後での意識変化：（図7）
親ががんを患った際に子どもに話す必要性について「とても必要」または「必要」と答えたのは、市民公開講座参加前では88名（98.9%）、参加後は89名（100%）となった。

(図7)子どもに話す必要性について



（2）親ががん患者である子どもに対するサポートの必要性：（図8）
周囲からのチャイルドサポートについて「とても必要」または「必要」と答えたのは、「医療関係者から」のサポートについては97名（97.0%）、「教育関係者から」のサポートについては98%（97.0%）、「保健・福祉関係者から」のサポートについては97名（96.0%）であった。

(図8)親ががん患者である子どもに対するサポートの必要性



（3）自分ががんを患った時の自身の心理的サポートの必要性
自分ががんを患った時の自身の心理的サポートについては、「ぜひ受けたい」45名（42.9%）、「受けたい」50名（47.6%）であった。

D．考察

Ⅰ．「夏休みキッズ探検隊」について

子どもについては、昨年と同様に、ほとんどの項目で高い評価を得ており、また、イベント介入前後の子どもストレスについても有意に軽減されており、イベントの目的の1つであった「病気や病院について正しく学ぶことにより不安が軽減され、レジリエンスが引き出される」については、ほぼ達成されたと考えられた。子どもの「自分のことを人に話す」という項目については、昨年と同様に他の項目に比して評価が低かったが、これはイベントが1回限りであり、子ども同士が話をする機会がやはり少なかったためと考えられた。

親の評価は、昨年と同様に子どもに比し

て低かったものの、「全体的に今回のイベントは良かった」との評価を得た。上記の子どもの評価と同様に、親も「子どもが成長したと感じる」「子どものがんに対する不安を和らげることに役立った」と感じており、「子どものいるがん患者の安心に役立った」との評価に結び付いたものと考えられる。

Ⅱ.「看護に活かすチャイルドケア～がん医療における子どもへの関わり方を学ぶ～」について

参加者の8割以上の参加者がチャイルドケアについては初めての受講であったが、ワークショップの前後で、がん医療における子どもの心理、行動に対する理解が深まっており、その必要性、理解については参加者の全員に行き渡ったと考えられた。また、32名（94%）が「自施設で実施可能なチャイルドケアに関する取り組みの参考になる」としており、臨床現場のニーズに即した内容であったことが推察される。実際に研修参加目的として、チャイルドケアに関わっている（今後関わる）または必要とするケースがあったということが挙げられており、今後県内の拠点病院や県内小児科病棟をもつスタッフに対して、ケース検討会、勉強会など、チャイルドサポートをテーマとした継続的な医療者支援が必要だと言える。

Ⅲ.市民公開講座つながるいのち～～がん医療の現場から～」について

参加者の背景として、女性、30 代～60代、職種別でも医療関係者に次いで主婦が多く、（まさに子育て中である方を含む）子育て世代の女性から多く参加いただけたものと思われた。また、がん経験については、「自分も家族も患者でない」が約半数（57名、49.1%）であり、がん経験がない市民にとっても関心が高いテーマであったことがうかがえた。一方、職種別では保健・福祉関係者 10 名（9.4%）、教育関係者 7名(6.6%)と、少数ではあるが参加があり、チャイルドサポートについて関心をもっていただけるようになってきたことがうかがえる。

親ががんを患った際に子どもに話す必要性について、市民公開講座参加前後で、「必要」または「とても必要」としたのが（後）（前）88.9%、（後）100%と意識変化をもたらしていた。

親ががん患者である子どもに対して、医療者、教育関係者、保健・福祉関係者からのサポートについてもほぼ全員が「とても必要」または「必要」とし、周囲からのサポートの重要性が認識されていた。

自分ががんを患った時の自身の心理的サポートについても、ほぼ全員が「ぜひ受けたい」または「受けたい」とし、やはり子どもに限らず患者自身についてのサポートが不可欠であると思われた。

以上より、がんになった(子育て世代の)「親」およびその「子ども」を含む「家族」に対して、診断・治療期からの継続的なサポートの提供が必要であると考えられた。その実現のためには、院内においては、外来・病棟の看護師を中心としたスタッフの協力が不可欠であり、今後もカンファレンスや勉強会での情報共有と啓蒙を進めていく必要があると考えられた。

また、そのような支援について病院など

一機関（施設）ができることはほんのわずかであるため、教育機関や地域保健機関やなどを含めた様々な立場の資源と連携し支援できる体制の整備が必要であると考えられ、今後は、特に教育関係者や保健・福祉関係者を含めた地域住民に対して広く情報発信し、協力体制を構築していく必要があると思われた。

がん診療連携拠点病院として、今後も患者・家族および医療関係者、地域へのサポートの提供および情報発信を行い、院内、院外、地域が協働して、がんになった「親」をおよびその「子ども」を含む「家族」を支えるしくみ作りをさらに推進したい。

E．結論

子どもを含めた家族に対する支援について病院でできることとして、昨年に引き続きがんになった親をもつ子ども（小学生）に対する認知行動療法に基づく心理教育プログラムであるⅠ.「夏休みキッズ探検隊」を内容を発展させて実施した。また、医療関係者を対象とした研修・ワークショップとしてⅡ.「看護に活かすチャイルドケア～がん医療における子どもへの関わり方を学ぶ～」を開催し、がん医療における子どもに対する関わり方について医療関係者の理解を深めた。さらに、Ⅲ.市民公開講座「つながるいのち～がん医療の現場から～」を開催し、望まれるチャイルドサポートの在り方について地域住民とともに考えた。がんになった（子育て世代の）「親」およびその「子ども」を含む「家族」に対して、診断・治療期からの継続的なサポートの提供が必要であるが、病院など一機関（施設）ができることは限られているため、今後も患者・家族および医療関係者、地域へのサポートの提供および情報発信を行い、院内、院外、地域が協働して、がんになった「親」をおよびその「子ども」を含む「家族」を支えるしくみ作りをさらに推進したい。

F．研究発表

1．論文発表

該当なし

2．学会発表

1）清藤佐知子、井上実穂、谷水正人：「がんになった親をもつ子どもに対する取り組み～チャイルドケアプロジェクト～」第56回 愛媛乳腺疾患懇話会. 平成25年5月11日. 愛媛県松山市

2）井上実穂、清藤佐知子、菊内由貴、谷水正人：「親ががん患者である子どもへの支援～チャイルドケアプロジェクトの効果検証（1）～」第18回日本緩和医療学術大会. 平成25年6月22日. 神奈川県横浜市

3）清藤佐知子：「がんになった親をもつ子どもに対する取り組み：チャイルドケアプロジェクト～治療期からのトータルケア～」第21回 日本乳癌学会学術総会. 平成25年6月27日. 静岡県浜松市

4）井上実穂、谷水正人：「親ががん患者である子どもへの心理教育プログラム『キッズ探険隊』の開発」第13回日本認知療法学会. 平成25年8月23日. 東京都豊島区

5）清藤佐知子、井上実穂：「『子育て世代のがん患者』の支援～チャイルドケアプロジェクト～」. 第51回 日本癌治療学会学術集会. 平成25年10月25

日．京都府京都市

6）井上実穂、宮内一恵、谷水正人：「院内全体で取り組むがん患者・家族への支援　チャイルドケアプロジェクト『夏休みキッズ探検隊』」第67回国立病院総合医学会.平成25年11月9日.石川県金沢市

3．その他の発表

1）医療関係者を対象とした研修・ワークショップ『看護に活かすチャイルドケア～がん医療における子どもへの関わり方を学ぶ～』開催:平成25年6月9日.愛媛県松山市、四国がんセンター

2）「夏休みキッズ探検隊」開催：平成25年8月7日.愛媛県松山市、四国がんセンター

3）市民公開講座開催『つながるいのち～がん医療の現場から～』開催：2014年1月11日.愛媛県松山市、松山市総合コミュニティセンター

G．知的財産権の出願・登録状況

1．特許取得

該当なし

2．実用新案登録

該当無し

3．その他

該当なし

愛媛県がん患者・家族支援推進事業
がん患者・家族支援に関する医療関係者向け研修会のお知らせ

看護に活かすチャイルドケア

～がん医療における子どもへの関わり方を学ぶ～

がん医療における子どもに対する関わり方について、チャイルドライフスペシャリスト（CLS）・医師・心理士から、その具体的な方法、技術を学ぶ研修・ワークショップです。

日時：平成25年6月9日（日）
9：30～16：30（受付9：00～）

場所：四国がんセンター
地域医療連携研修センター3階研修室

CLSとは…
アメリカで取得できる専門資格で、発達心理学、家族学などを基礎に、医療環境にある子どもや家族に対して心理社会的支援を行う医療スタッフです。日本では30名ほどのCLSが活躍しています。（四国には不在）

内容：年齢に応じた子どもの病気や死に対する理解をもとに、子どもや家族に用いられるアクティビティ（工作など）の実習を行います。
事例検討、子どもへの心理教育プログラムの紹介など、現場に役立つ内容です。

講師：石田也寸志（愛媛県立中央病院　小児医療センター長）
井上　絵未（済生会横浜市東部病院こどもセンター　CLS）
井上　実穂（四国がんセンター　臨床心理士）
村瀬有紀子（東京医科歯科大学附属病院　小児科　CLS）

◆事前申込み必要
（裏面をご参照ください）

対象：看護師、ほか職場で子どもと接する機会がある医療従事者
定員：先着50名
応募〆切：平成25年5月24日（金）
参加費：無料

お問い合わせ：四国がんセンター 患者・家族総合支援室
TEL　089-999-1111（代表）
Mail　kensyuh@shikoku-cc.go.jp
※メールにてお問い合わせの場合、
件名を「チャイルドケア問合せ」
として送信をお願いします。

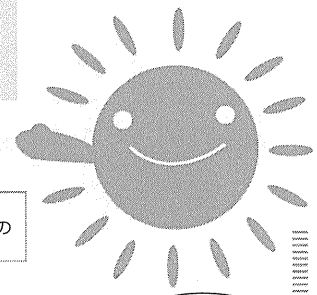
独立行政法人国立病院機構
主催　四国がんセンター（患者・家族総合支援センター）

愛媛県がん患者・家族支援推進事業

チャイルドケアプロジェクト Child Care Project

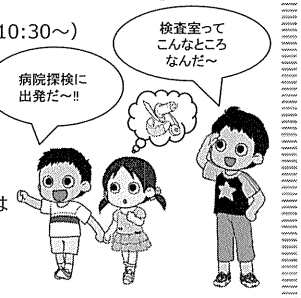
夏休みキッズ探検隊

愛媛県では、がん患者の治療、療養が円滑に行われるために、子どもを含めた総合的支援に取り組んでいます。
このイベントは、親ががん患者である子どもが、同じ立場の仲間と出会うこと、がんに対する理解を深めること、医療関係者との関わりを持つことなどを通じて、病院や病気に対する怖さや不安を和らげ、さらには家族内のコミュニケーションの促進や、子どもが本来持っている困難を跳ね返す力を高めることを目的としています。

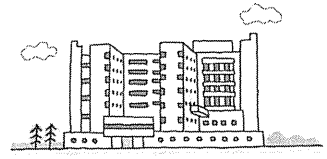


［対　象］　小学1～6年生
四国がんセンターの患者さんのお子さんで、親ががんであることを知っており、イベントへの参加を希望していることが条件となります。

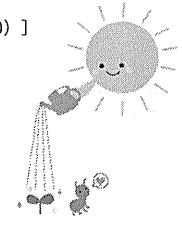
［定　員］　10名
［日　時］　平成25年8月1日（木）11:00～16:00（受付10:30～）
［場　所］　四国がんセンター
［内　容］　①がんについて学ぼう！
②病院内を探検しよう！など
※このイベントはお子さんのみの参加となっております。
［参加費］　無料
［申込方法］　申込書・アンケートにご記入の上、郵送または直接ご持参ください。
［応募締切］　平成25年7月19日(金)　当日消印有効
(持参の場合は、当日17:00まで)
※ただし、定員に達し次第、締め切りとさせていただきます。



＊申込書は…患者・家族総合支援センターまたは、がん相談支援・情報センターにあります（病院HPからもダウンロードできます）



［申込み・問い合わせ（平日8：30～17：00）］
独立行政法人国立病院機構
四国がんセンター
患者・家族総合支援センターまたは、
がん相談支援・情報センター
「夏休みキッズ探検隊」係
〒791－0280　愛媛県松山市南梅本町甲160
TEL：089－999－1209（直通）



市民公開講座

つながる いのち

～ がん医療の現場から ～

厚生労働科学研究(がん臨床研究)推進事業

共催 ： 公益財団法人 日本対がん協会
愛媛県がん診療連携協議会
四国がんセンター

入場無料

日時 2014 年 **1** 月 **11** 日（**土**）
12:30 ～ 16:00（受付 12:00 ～）

会場 **松山市総合コミュニティセンター**
3階　大会議室　(松山市湊町7丁目5番地)

定員 250名（先着順）

プログラム

総合司会　四国がんセンター　清藤 佐知子 乳腺科医師

第一部 12:30～14:30　【映画上映】『うまれる』

第二部 14:50～16:00

【講演】「親ながん患者である子どものこころ　～研究結果をふまえて～」
聖路加国際病院　小澤 美和 小児科医長

【対談】「子ども達と過ごした日々　～経験者からのメッセージ～」
松山記念病院　大舘 千恵 看護師
NPO法人愛媛がんサポートおれんじの会　松本 陽子 理事長

【講演】「大切な人をなくした子どもたちを支える　～こころを癒やす絵本の紹介～」
四国がんセンター　井上 実穂 臨床心理士

お問い合わせ お申し込み

四国がんセンター・平松　平日13:00～17:00
TEL:089 – 999 - 1111 (内線：7535)

☆詳細は裏面をご覧ください

映画『うまれる』は、妊娠・出産・育児を通じて、私たちがうまれてきた意味や家族のあり方、そして“生きる”ことを考える、ドキュメンタリー映画です。見ていただいた方々の全細胞の隅々にまで、いのちのすごさが染みわたる、そんな映画にしたいと思い、毎日、魂を込めてつくってきました。ぜひ、ご覧ください。
(企画・監督・撮影　豪田トモ氏のコメントより)

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
小澤美和	子育て中のがん患者とその子どもの心	がん看護	18 (3)	373-376	2013
小澤美和.	小児がん患者と家族および、子育て世代のがん患者とその家族の支援 がん患者とその子どもたちの現状と支援	小児保健研究	72 (2)	217-219	2013
阿佐美百合子, 小澤美和	実践領域に学ぶ臨床心理ケーススタディ 臨床心理ケーススタディ 1)コアから思考する 医療 総合病院小児科領域の心理臨床	臨床心理学増刊号	5	82-87	2013
東飛鳥, 小林明雪子, 小澤美和, 細谷亮太	幹細胞移植ドナー候補となったきょうだいに対するトラウマの視点からの心理的評価	子どもの心とからだ	22 (1)	63-68	2013
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Ⅳ.　研究成果の刊行物・論文別刷

第59回日本小児保健協会学術集会　シンポジウム2

小児がん患者と家族および，子育て世代のがん患者とその家族の支援

がん患者とその子どもたちの現状と支援

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Ⅰ．はじめに

2006年の米国がん統計[1]では，がん患者の24％は18歳未満の子どもがいる，と言う。とくに，乳がん，子宮頸がんなどの若年発症が増加していることが示され，例えば，55歳未満の乳がん患者の1／3には，学校に通う年齢の子どもがいるのである。

近年，がん診療におけるトータルケアの重要性が唱えられ，国の政策により浸透してきているが，家族の中にこれだけの頻度で子どもが存在しているにもかかわらず，子どもを視野に入れた家族ケアは，行われてこなかった。

しかしながら，がん患者であり子育て中の親たちは，闘病生活の中での心配は，家族の中での役割を継続し，子どもにとって良い親であり続けたいと思いながら，子どもへの説明をどうしたらよいかと悩んでいることが報告[2]されている。

小児医療に携わる私たちは，患者・家族側の現状を知り，医療者側の事情と合わせて，がん診療が行われている傍らにいる子どもたちのためにできることを考え，成人診療領域との連携を行う必要がある。

Ⅱ．がん臨床における子ども支援

2010年に，日本乳がん学会会員に，子どもへの介入（心理的支援）に関する意識調査を行った[3]。乳がん学会専門医898名，乳がん看護認定看護師135名に送付し，回収率はそれぞれ約35％，50％であった。結果を，図1に示した。

このアンケートから，子どもへの介入をした方がよい，もしくはすべきと考えている医療者が約7割いる一方で，実際には8割以上ができていないとの回答であった。この傾向は，2009年にがん診療における研修会，講演会に参加した看護師，ソーシャルワーカー，心理士ら245名から得た回答でも同様で，約95％が介入すべきもしくはした方がよいと思いながらも，約80％が実践できていない，という現状であった[4]。

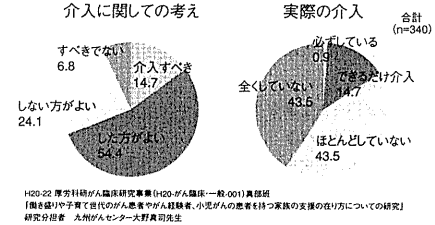

図1　乳がん診療における子どもへの介入に関する意識調査

子どもへの心理的支援をしない方がよいという理由の自由記載を表[3]にまとめた。子どものサポートに関する知識がない，という理由がもっとも多かった。

また，子育て中のがん患者の現状を，筆者の施設においてまとめたものが，図2である。2008年8月～2011年11月の約2年の間に，子育て中の乳がん患者356例と面談をしたところ，42％が親の闘病が子どもに与える影響を心配し，35％が子どもへの説明について悩んでいた。このうち9％が子どもとの面談を希望され，病状の進行により7％が子どもを対象としたグリーフワークに関わった。

闘病中の親にとって子どもの存在は，自身の生活を

聖路加国際病院小児科　〒104-8560 東京都中央区明石町9-1
Tel：03-3541-5151　Fax：03-3547-3330

表　子どもへの心理的支援をしない方がよい理由

子どものサポートについて知識がない
介入が適切かどうか判断できない
医師，看護師どちらが介入すべきかわからない
過干渉
状況に合わせるべき
患者の病状により変わる
家族の状況により変わる
反応を知る必要性
介入後の反応を知ることができない
患者の了承を得てから介入する必要がある
サポート体制
診療報酬がつかない
十分な時間を費やせない
体制が不十分
専門家に任せるべき
家族の問題
プライベートすぎる
家族に任せるべき
両親が子どもに真実を伝えたがらない
介入することで子どもが不利益を被る可能性

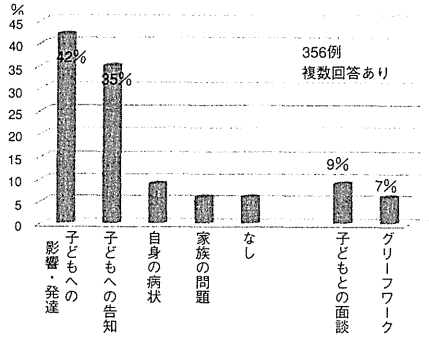

図2　乳がん患者からの相談内容

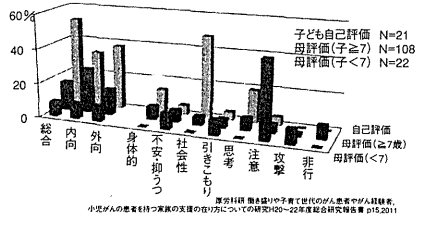

図3　乳がん患者の子どもの情緒・行動の問題

考えるうえで大変重要であることがわかる。がん診療におけるトータルケアが重要視されるようになった今日，子どもを視野に入れた支援は欠かせないと言える。

Ⅲ．がん患者を親に持つ子どもの情緒・行動

Osborn[5]は，がん患者とその子どもに関する10の調査報告（1994～2005年）をレビューしている。半分の報告は100%，残り５つの報告は80%以上が，母親ががん患者である集団とその子どもの調査である。がん患者を親に持った子どもはおおむね心理・社会的な問題はないものの，わずかに内向性の問題を持つリスクが高い，とまとめている。また，乳がん患者を親に持つ子どもを対象群・そのクラスメートを比較群にした調査では，男児の方が集団に存在するうえでの感受性が高く，孤立しやすいという報告[6]や，両親が辛いと感じている場合にその子どもは内向性が高い行動をとるという報告[7]がある。その他，家族の凝集性の低さは子どもの外向性を，母親の抑うつ状態は子どもの内向性を助長しているという報告[7]などもあり，親や家族の状態が関連因子として挙げられている。一人親家庭，きょうだいの数が少ない，第１子，学童期の子どもたちは，有意に情緒・行動の問題が生じやすいとも言う[8]。

また，母親のがんに関する統計学的因子，例えば診断されてからの期間，治療内容は，子どもの心理状態とは，明らかな関係は認められていない[5]。

国内の現状は，筆者の単施設の報告[4]であるが図３に示したとおりである。これは，乳がん患者130人（30～52歳）とその子どものうち協力が得られた７歳以上の子ども21人による情緒・行動の問題を質問紙（子どもの行動チェックリスト，ユースセルフレポート）によって調査した結果，各項目について臨床域・境界域を合わせた割合を示したものである。約半分の子どもたちが自分の情緒・行動について総合的に問題意識がある一方で，親からみた子どもの総合評価では，約15%しか問題意識がないという親子での認識の差があることが示された。とくに７歳以上の子どもの自己評価では，社会性の問題の頻度が高く，幼児期の親評価では注意・集中の問題の頻度が高いという特徴がみられた。

そして，親自身のソーシャルサポートの享受感が低い（$p<0.01$）と，また，親の不安・抑うつが高い（$p=0.018$）と子どもの問題を親が気にしやすい傾向が認められた[4]。

がん患者である親自身の心理社会的サポートを行いつつ，親子での認識に差があることを意識して，がん患者に子どもの様子を尋ねる一言が，がん患者を親に持つ子どもへのサポートを始めることにつながると言えるだろう。

Ⅳ．がん患者を親に持つ子どものストレス反応

海外の報告[6]では，母親が乳がん患者であることのストレス反応は男児（33%）よりも，女児（45%）の方が高いと言う。また，再発がんの母親を持つ娘たちの方が初発のがん患者である母親を持つ娘たちよりも高いストレス反応を示していた[7]と言う。また，小児期に自分の親ががん患者として闘病していた経験のある成人に，当時を振り返る面接をした報告[9]では，病気になった親との関係がよくなり，家族全体の力も増して，心的外傷後成長の理論に合致するような状態であったと言う。

国内では，前述の厚労科研の報告[4]を引用すると図４の通りである。乳がん患者である母親125人とその子ども６歳以上に，心的外傷後ストレス症状の有無を尋ねる質問紙調査（親：Impact Event Scale-Reviced，子ども：Posttraumatic stress disorder-Reaction Index）を行った。

乳がん患者である親は，約半分がカットオフ値を超える心的外傷後ストレス症状（PTSS）を呈していた。その子どもたちにおいては，親が病気になった体験に関するPTSSを，親と同じく半分以上が呈していた。子どもたちは自分が病気でなくとも，親と同頻度でPTSSを呈しているということは，家族ケアを行う際には子どもに関する支援が必須であることを示唆していると言える。

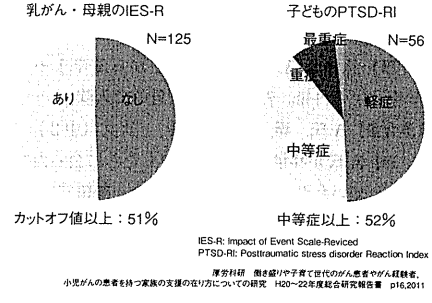

図4　がん患者とその子どもの心的外傷後ストレス症状

Ⅴ．おわりに

成人がん診療領域においては，トータルケア・家族ケアが浸透してきた一方で，子どもは未知なる存在であるために，子どもを視野に入れたケアはようやく端緒についたばかりと言える。この連載を通して，闘病中のがん患者とその子どもについて知り，今後の子どもへの支援が広がっていくことが望まれる。

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bjh research paper

Secondary cancers among children with acute lymphoblastic leukaemia treated by the Tokyo Children's Cancer Study Group protocols: a retrospective cohort study

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Summary

With improvement in survival, it is important to evaluate the impact of treatment on secondary cancers in acute lymphoblastic leukaemia (ALL) survivors. A retrospective cohort study comprising 2918 children diagnosed with ALL and enrolled on Tokyo Children's Cancer Study Group (TCCSG) protocols between 1984 and 2005 was conducted to evaluate the incidence of secondary cancers and associated factors including treatment protocol, cranial irradiation and other characteristics of the primary ALL. Thirty-seven patients developed secondary cancers, including acute myeloid leukaemia (n = 11), myelodysplastic syndrome (n = 5), non-Hodgkin lymphoma (n = 2), brain tumours (n = 13) and other solid carcinomas (n = 6) within a median follow-up duration of 9·5 years. The cumulative incidence of any secondary cancers was 1·0% (95% confidence interval (CI), 0·7–1·4%) at 10 years and 2·4% (95% CI, 1·5–3·7%) at 20 years, respectively. Standardized incidence rate ratio of secondary cancers was 9·3 (95% CI, 6·5–12·8). Multivariate analyses showed an increased risk of secondary cancers associated with the recent treatment protocol and cranial irradiation. There was no evidence of a reduction in secondary cancer incidence despite marked decreases in cranial irradiation use in the recent protocols.

Keywords: secondary cancers, acute lymphoblastic leukaemia, children, cumulative incidence, standardized incidence rate ratio.

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Intensive multidrug therapy has steadily improved the overall survival (OS) of children with acute lymphoblastic leukaemia (ALL) despite decreasing prophylactic cranial irradiation (Pui *et al*, 2009; Tsuchida *et al*, 2010). The immunosuppressive and cytotoxic therapy necessary to achieve this improvement increases the risk of subsequent late effects. One of the most serious late effects is the development of a secondary cancer.

Reports from previous studies including the Childhood Cancer Survivor Study (CCSS) and British CCSS (BCCSS) have contributed important evidence regarding the risk of subsequent primary neoplasms among survivors of childhood cancers, such as ALL.(Hawkins *et al*, 1992; Neglia *et al*, 2001; Mody *et al*, 2008; Meadows *et al*, 2009; Friedman *et al*, 2010; Reulen *et al*, 2011) However, the study populations comprising both of these large cohorts are childhood cancer patients who have survived at least 5 years following primary cancer diagnosis and the results do not account for the time at risk during the first 5 years.(Hawkins & Robison, 2006).

A few studies have described the overall risk of secondary cancers among children with ALL with the period of observation beginning from a time shortly following successful complete remission (CR). (Neglia *et al*, 1991; Nygaard *et al*, 1991; Kimball Dalton *et al*, 1998; Loning *et al*, 2000; Bhatia *et al*, 2002; Hijiya *et al*, 2007; Schmiegelow *et al*, 2009) Compared with the general population, the survivors with a history of childhood ALL have been estimated to have a 10- to 20-fold greater risk of developing a secondary cancer. In addition to genetic predisposition, previously administered chemotherapy and/or radiotherapy are considered the most important risk factors. (Loning *et al*, 2000) Based on the cohort of patients previously enrolled onto a Tokyo Children's Cancer Study Group (TCCSG) protocol since 1984, the current study is the first report from an Asian country to describe the incidence and types of secondary cancers observed among survivors of childhood ALL. We also aimed to evaluate potential risk factors for secondary cancers, particularly the influence of treatment protocol and cranial irradiation use.

Patients and methods

Study population

A total of 2,918 newly diagnosed children with ALL aged 1–15 years were entered into 5 consecutive TCCSG studies between 1984 and 2005 (L84-11, L89-12, L92-13, L95-14, and L99-15/L04-1502; Figure S1). The current analysis was primarily based on 2,807 patients who underwent a successful induction phase, achieved CR and survived for at least 2 months or more in the intention-to-treat group, including a total of 621 stem cell transplantations (SCT) had been performed for the primary ALL during the observation period of the study population (Fig 1). Details of the treatment regimens and main therapeutic results have been previously published. (Tsunematsu *et al*, 1974; Toyoda *et al*, 2000; Manabe *et al*, 2001; Igarashi *et al*, 2005; Hasegawa *et al*, 2012) Although the patients in our cohort were treated according to therapeutic protocols, we do not have detailed information regarding actual doses of additional therapeutic exposures given to the relapsed patients, which potentially could have influenced the development of secondary cancers. As a sensitivity analysis, we conducted the same analysis on 1716 patients (referred to as the per protocol group), limited to the patients who had completed all planned treatment leading to first CR (Fig 1).

The cumulative doses of the important treatment contents are listed in Table I. The cumulative anthracycline dose was converted to doxorubicin (DOX)-equivalent doses, which ranged from 0 to 415 mg/m^2. The cumulative cyclophosphamide (CPM) dose ranged from 0 to 6·8 g/m^2 and etoposide (up to 2·4 g/m^2) was administered in only some ALL high-risk regimens. The actual doses of oral drugs given to the patients, such as methotrexate and mercaptopurine (6-MP) were adjusted by white blood count (WBC) counts; therefore we evaluated maintenance duration in our analyses instead of oral antimetabolites doses. A major change over time across the TCCSG treatment protocols included a decrease in the executed proportion and dosage of prophylactic cranial radiation therapy (CRT) and intensified systemic and intrathecal chemotherapy. Prophylactic CRT was part of the treatment protocol for all patients in the L84-11 trial, whereas only 8·6% of the patients in the more recent L99-15/L04-1502 trial received CRT, which was limited to the high-risk group (Table I).

Follow-up and data collection

Follow-up of the patients were performed by the treating institution every 2 years, at which time any late effects including secondary cancer were documented into the TCCSG database. To obtain additional information on characteristics of the secondary cancer diagnosis, we distributed a survey to the treating institution to collect data on the date of diagnosis, cytological or histological characteristics including cytogenetic findings, cancer site, cumulative treatment exposures before secondary cancers, treatment contents given for secondary cancers and its outcomes. The time at risk for secondary cancers was computed from the date of ALL diagnosis to the date of secondary cancer diagnosis, date of death or date of last contact, whichever came first. The end of follow-up for the study was December 2011.

Statistical analysis

Cumulative incidence of secondary cancers over time was calculated using competing risk methods (considering any death as a competing event).(Gooley *et al*, 1999) The incidence rates of cancer in the Japanese general population (obtained from the regional cancer registry of National Cancer Centre Hospital in Japan) (Japanese National Cancer Centre Hospital, 2013) were used to calculate the number of cancers expected to occur in the patient cohort by calculating the total person-years at risk by gender and 5-year age

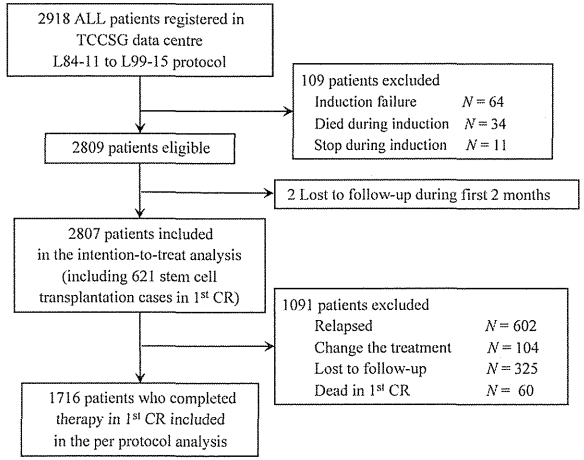

Fig 1. Flow diagram describing the criteria for patient selection. Total of 2918 newly diagnosed children with ALL aged 1–15 years entered into 5 consecutive Tokyo Children's Cancer Study Group (TCCSG) studies (L84-11, L89-12, L92-13, L95-14 and L99-15/L04-1502. The current analysis is primarily based upon 2807 patients who successfully acheived complete remission (CR) and survived at least 2 months or more as the intention-to-treat analysis. 1st CR, first complete remission.

groups and multiplying by the corresponding cancer rates observed in the general population. The standardized incidence rate ratio (SIR), defined as the ratio of the number of observed cancers divided by the number of expected cancers, was used to evaluate the difference in cancer occurrence between the ALL group and the general population. Absolute excess risk (AER) was calculated as the difference between the number of observed events and expected events divided by the number of person-years of follow-up, and was expressed as per 100 000 person-years. Survival analysis was conducted using Kaplan-Meier methods (Log-rank method for comparison) and Cox regression model for hazard ratio (HR) estimates. Variables examined in the regression model included age at ALL diagnosis, risk classification, age at last follow-up, CRT (yes or no), specific anti-cancer agents (yes or no), and duration of maintenance therapy. Treatment protocol and the anticancer agents could not be entered as co-variable factors in the same regression model due to their highly correlated nature. Thus, treatment protocol was included in the main analysis, but the same model replacing protocol with the anticancer agents was also performed to evaluate their effects. Data were analysed using the SPSS statistical software, version 20.0 (IBM Japan Ltd., Tokyo, Japan) and EZR (Saitama Medical Centre, Jichi Medical University), a graphical user interface for R. (Kanda, 2013).

Results

The OS proportions of the TCCSG ALL L84-11 to L04-1502 protocols are shown in Table I. Ninety-seven percent of the whole study population achieved CR and 602 (21·4%) of the 2,807 children among the intention-to-treat group suffered a relapse. Of the total patients, about 70% were followed until after 2008. Even with reduction in CRT use, from 100% to 8·6%, 10-year OS has increased steadily from 74% to more than 85%. The median follow-up duration after diagnosis of ALL was 9·5 years (range 0·2–27 years), with a total of 27 495 person-years of follow-up. At December 2011, a total of 37 secondary cancers had been diagnosed in our cohort, including acute myeloid leukaemia (AML, n = 11), myelodysplastic syndrome (MDS, n = 5), non-Hodgkin lymphoma (NHL, n = 2), brain tumours (n = 13) and other solid carcinomas (n = 6).

Cumulative incidence

The overall cumulative incidence of secondary cancers was 1·0% (95% confidence interval [CI], 0·7–1·4%) at 10 years, 1·4% (95%CI, 0·9–2·0%) at 15 years and 2·4% (95%CI, 1·5–3·7%) at 20 years from the diagnosis of ALL, respectively (Fig 2A). The corresponding cumulative incidence among patients remaining in first CR was 3·9% at 20 years (95% CI: 2·3%–6·1%), which was significantly higher (P < 0·001) than patients not in first CR (Fig 2B). The cumulative incidence in persons who received CRT was 2·9% at 20 years (95% CI, 1·8–4·4%), which appeared higher than the patients without CRT (P = 0·057, Fig 2C). There was no statistically significant difference in cumulative incidence by TCCSG therapeutic protocol (Fig 2D).

Clinical characteristics of secondary cancers

The clinical characteristics of the patients with secondary cancers are summarized in Table II according to type of secondary cancer. Females were predominant (75%) in secondary AML/MDS. Types of secondary cancers differed also according to the age at diagnosis of ALL; brain tumours and

Table I. Cumulative doses of selected chemotherapeutic agents and radiation of ALL trials L84-11 to L99-15 according to risk groups.

Risk Group by protocol	Patients (n)	Anthracycline (mg/m²)						CPM (mg/m²)	VP-16 (mg/m²)	IV MTX (g/m²)	Maintenance (weeks)	MTXIT	CRT (Gy)	CRT rate (%)	10-year OS (%)
		DNR	DOX	THP	ACR	MIT	Total								
L84-11	484													100	74·3 ± 2·0
SR (A/B arm)†	194	0	0	0	0	0	0	0	0	2/3·5	172	9/15	18	100	
HR (A/B arm)†	244	180	0	0	150	0	224	6800/6000	0	1/2·5	172	5/11	24	100	
HEX	48	75	100	0	0	0	162	4000	0	0	96	11	24	100	
L89-12	418													80	73·5 ± 2·2
SR (A/B arm)†	142	0	100/0	100/150	0	0	160/90	0	900	9	91	9/9	0 vs 18	44	
IR	100	0	0	210	60	0	135	3100	2400	6	91	7	18	100	
HR	146	0	0	240	60	20	210	3600	2400	6	87	6	18	100	
L92-13	347													44	77·9 ± 2·2
SR	124	0	0	150	0	20	170	0	0	6	24	8	0	0	
HR (A/B arm)†	122	0	0	100	0	20	140	1000	1200	6/0	22	10	0 vs 12/18	47	
HEX	101	0	0	100	0	40	220	1000	1200	0	16	9 (6)	18	100	
L95-14	597													44	82·0 ± 1·6
SR	231	0	0	100	0	0	60	2000	0	10·6	54	11	0	0	
HR (A/B arm)†	129	0	0	220	0	0	132	4000	0	10/1	54	8	0 vs 12/18	18	
HEX	237	100	200	220	0	0	415	4000	0	1	54	8	18	100	
L99-15/L04-1502	1007													8·6	87·6 ± 1·2‡
SR	381	100	0	0	0	0	83	2000	0	13·15	104	11	0	0	
HR (A/B arm)†	404	100	100	120	0	0	245	4000/5000	0	10	52	10/11	0	0	
HEX	242	100	0	0	0	20	163	5600	1000	6	54	17	12/18	27·4	

SR, Standard risk; IR, Intermediate risk; HR, High risk; HEX: extremely high risk; DNR, daunorubicin; DOX, doxorubicin; THP, pirarubicin; ACR, acracinomycin; MIT, mitoxantrone; Total, DOX-equivalent dose; CPM, cyclophosphamide; VP-16, etoposide; MTX, methotrexate; CRT, cranial irradiation; IT, intrathecal; OS, overall survival.
†(A/B arm): cumulative doses of A arm/B arm; Additional details of treatment regimen are provided as supplemental information.
‡4-year overall survival rate.

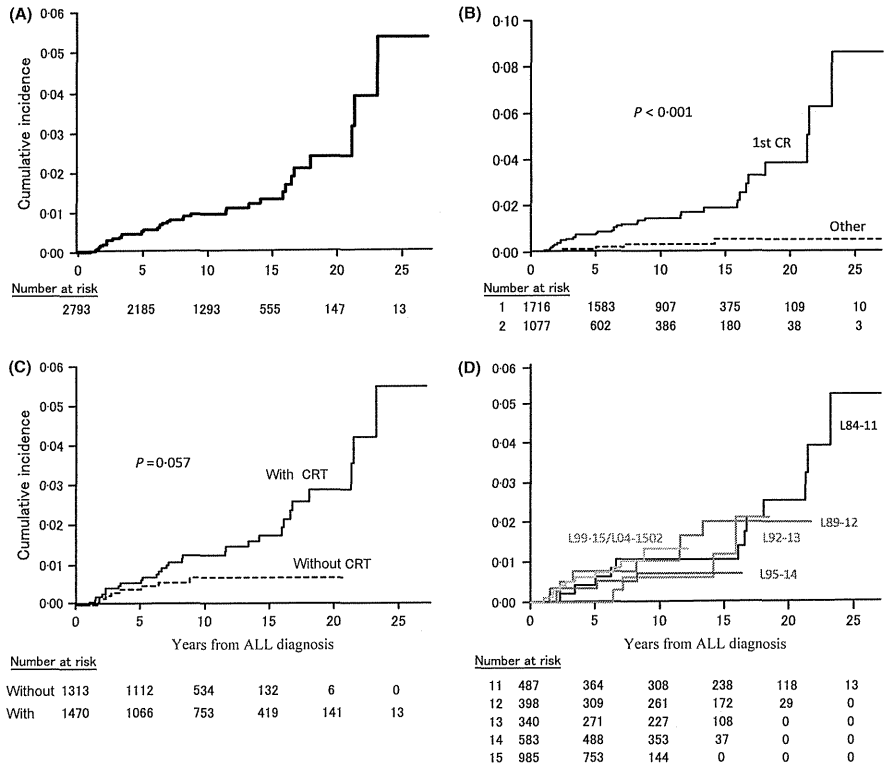

Fig 2. Cumulative incidence of secondary cancers. Shown are the cumulative incidences of secondary cancers as a function of time since primary ALL diagnosis over a maximum follow-up of 27 years. (A) Overall cumulative incidence of secondary cancer among the total patient cohort. (B) Overall cumulative incidence of patients remaining in first complete remission (1st CR) compared to others. (C) Overall cumulative incidence according to treatment with or without cranial radiation therapy (CRT). (D) Overall cumulative incidence according to treatment protocols: L84-11 (black line), L89-12 (red line), L92-13 (green line), L95-14 (purple line), and L99-15/L04-1502 (blue line). The numbers of patients at risk at a specific time point are indicated below each of the four plots.

other carcinoma tended to develop more commonly in children that were older at ALL diagnosis. There was no difference between types of secondary cancers with regard to initial WBC, immunophenotype and risk classification of the primary ALL. The median latency period from ALL diagnosis to secondary cancers was 6 years (range 1–23 years) and varied by type of secondary cancer (Fig 3). The median time to diagnosis for haematological cancers (AML, MDS and NHL) was shortest (median 3·0 years), followed by brain tumours (median 11·5 years) and other solid carcinoma (median 16·3 years). Haematological cancers developed most commonly during the first 10 years followed by brain tumours from 15 to 20 years (Fig 3A, B). The age distributions at diagnosis of secondary cancers are shown in (Fig 3C). Median age at diagnosis of secondary was earlier for haematological cancers than brain tumour (median 14 years) and other carcinomas (median 19 years). Among AML, the most common morphological type was M5 (3 had t (9;11) (p22;q23) with *MLL-MLLT3* translocation). Four MDS cases showed chromosomal abnormality. Lymphoma and solid tumours did not show any chromosomal abnormalities.

As for the characteristics related to the treatment of primary ALL, the secondary cancers with the highest proportions of patients who underwent CRT were MDS, brain tumour and other carcinoma, while the haematological cancers showed elevated cumulative anticancer drug doses. Among a total of 621 SCT that had been performed for the primary ALL during the observation period of the study population, only 3 patients

Table II. Clinical characteristics of patients with secondary cancers.

	AML	MDS	NHL	Brain tumour	Other carcinoma
Total number of secondary cancers	11	5	2	13	6
Gender (Male:Female)	3:8	1:4	2:0	8:5	3:3
Primary ALL					
Age at diagnosis of ALL (years)	5 (1–14)	5 (2–13)	4 (2–6)	8 (2–12)	11 (3–14)
Initial WBC count ($\times 10^9$/l)	20·5 (1·9–168)	11·2 (2·9–70)	8·7 (3·4–14)	12·6 (1·9–112)	4·9 (2·1–163)
Immunophenotype (B:T:Other)	7:0:4	3:0:2	2:0:0	7:1:5	6:0:0
Risk group (SR:IR:HR)	1:8:2	1:2:2	2:0:0	1:10:2	2:4:0
Secondary cancer (SC)					
Incubation time to SC (years)	3·3 (1·6–11·6)	2·3 (1·0–6·3)	3·1 (2·8–3·4)	11·5 (2·3–23·2)	16·3 (7·2–21·4)
Diagnosis on therapy	4/11 (36%)	2/5 (40%)	1/2 (50%)	0/13 (0%)	0/6 (0%)
Age at diagnosis of SC (years)	9·0 (6·4–21·3)	11·1 (4·0–14·5)	7·5 (5·3–9·7)	18·5 (10·3–27·7)	23·9 (18·8–32·6)
Sub-classification	M4: 2, M5: 7, M7: 1, Unknown: 1	RAEB: 1, CMML: 2, Unknown: 2	Diffuse large B-cell lymphoma: 1, Burkitt lymphoma: 1	Glioma: 8, Meningioma: 3, Other: 2	Oral cancer: 2, parotid cancer: 2, breast cancer: 1, thyroid cancer: 1
Treatment for primary ALL					
Protocol (11:12:13:14:15)	1:3:0:2:5	2:1:0:1:1	0:0:0:0:2	6:3:1:1:1	3:0:2:0:1
Cranial irradiation	6/11 (55%)	5/5 (100%)	0/2 (0%)	13/13 (100%)	5/6 (83%)
Dose of cranial irradiation (Gy)	18 (0–28)	18 (18–24)	24 (18–36)	0	18 (0–24)
Anthracyclines (DOX equivalent)	230 (50–330)	72 (0–190)	112 (82–142)	120 (0–190)	47 (0–230)
Cyclophosphamide ($\times 10^3$ g)	4·0 (3·1–6·0)	4·0 (0–5·6)	1·0 (0–2·0)	4·0 (0–6·8)	1·1 (0–6·0)
Etoposide ($\times 10^3$ g)	0 (0–2·4)	0 (0–2·4)	0 (0–2·4)	0	0 (0–1·2)
Duration of maintenance (weeks)	52 (28–172)	96 (62–172)	96 (22–175)	78 (52–104)	112 (0–172)
Stem cell transplantation	0	0	0	1/13 (8%)	2/6 (33%)
Treatment for secondary cancer (SC)					
Surgery	0	0	0	9	6
Radiation	0	0	0	7	3
Chemotherapy	11	4	2	6	3
Stem cell transplantation	8	1	0	0	0
Median survival duration (years)	1·7 (0·2–4·3)	4·6 (0·9–11·1)	3·6 (0·5–6·7)	2·0 (0·1–11·3)	3·0 (0·8–10·4)
4 year survival rate (%)	24%	60%	50%	50%	83%
Standardized incidence ratio (SIR) and absolute excess risk (AER)					
No. observed/expected	16/0·64	2/0·52	13/0·36	6/2·45	
SIR (95%CI)	25 (14–41)	3·8 (0·5–14)	36 (19–62)	2·5 (0·9–5·3)	
AER/100 000 person-years	118	9·4	90	26	

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; RAEB, refractory anaemia with excess blasts; CMML, chronic myelomonocytic leukaemia NHL, Non-Hodgkin lymphoma; WBC, white blood cell; SR/IR/HR, standard/intermediate/high risk; DOX, doxorubicin; 95% CI, 95% confidence interval.
Numbers shown as median (range; minimum-maximum).

developed a secondary cancer (1 brain tumour and 2 other cancers). All 3 cases received total body irradiation-containing conditioning regimens, two of 3 developed tongue carcinoma whilst suffering from chronic graft-versus-host disease after allogeneic SCT. SCTs were common among secondary AML patients as treatment. Kaplan–Meier OS curves for the patients with secondary cancers are shown in (Fig 3D). The lowest survival probabilities were observed for patients with AML/MDS/NHL compared to patients with brain tumours and other carcinoma (P = 0·045 by log-rank test).

SIR and AER

We compared the incidence of secondary cancers in our cohort with that of the general population using the regional cancer registration database of the National Cancer Centre Hospital in Japan. As shown in Table II, the SIR was 25 (95% CI, 14–41) for AML/MDS, 3·8 (95% CI, 0·5–14) for lymphoma, 36 (95% CI, 19–62) for brain tumours and 2·5 (95% CI, 0·9–5·3) for other solid carcinoma. This represents a 9·3-fold (95% CI, 6·5–12·8) increase risk of all secondary cancers during a total of 27 658 person-years of observation. The total AER for secondary cancers was 256 per 100 000 person-years.

Risk factors for secondary cancers

The unadjusted analyses comparing patients with and without secondary cancers showed differences in age at ALL diagnosis, risk classification, CPM and CRT, while there were no statistically significant differences with respect to gender,

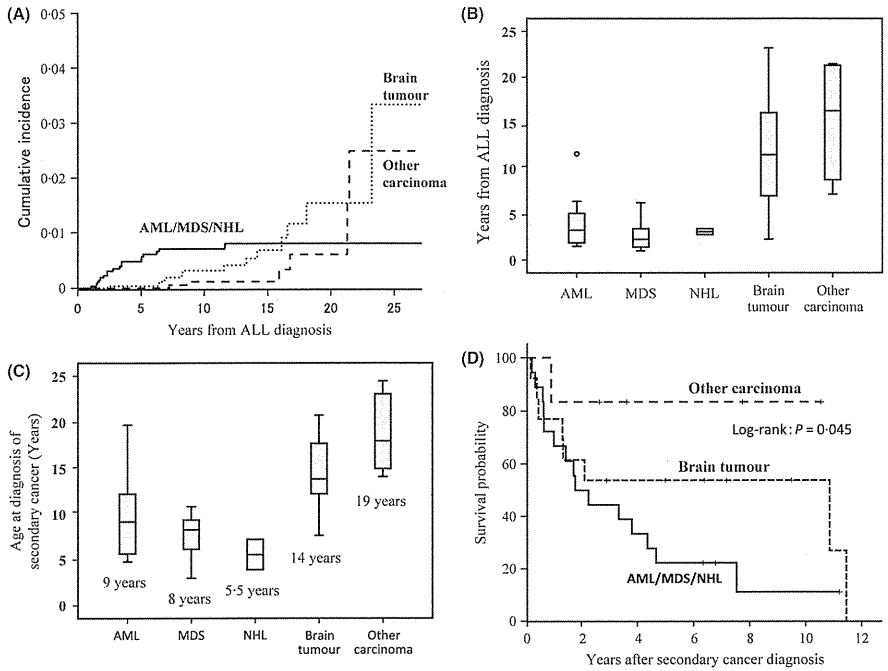

Fig 3. Clinical characteristics according to types of secondary cancer. (A) Cumulative incidence by years since ALL diagnosis of specific secondary cancers including AML/MDS/NHL (solid line), brain tumour (dotted line), and other carcinoma (dashed line). (B) The median latency period from diagnosis of ALL to development of specific secondary cancers. The median time for haematological cancers (AML, MDS and NHL) was shortest, followed by brain tumours and other solid carcinoma. (C) Age at diagnosis of secondary cancers; generally, the median age of haematological cancers was younger compared to brain tumours and other carcinomas. (D) Overall survival of secondary cancer patients are shown using Kaplan–Meier survival curves. Survival probabilities were the lowest for patients with AML/MDS/NHL. Actuarial survival at 4 years from diagnosis of secondary cancers depend on the type; AML/MDS/NHL 33%; brain tumours 54%; other carcinoma 83%. AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma.

initial WBC, immunophenotype, anticancer agents (with the exception of CPM) and maintenance duration of the primary ALL (Table III and Figure S2). Because protocol and anticancer drugs were highly correlated, we were unable to effectively evaluate them in the same multivariate regression analysis. Thus, results using Cox regression adjusting for covariates including treatment protocol (but not anticancer drug) (Table III) showed that CRT was associated with a 6-fold increased risk of secondary cancers compared to patients not receiving CRT (HR = 6·02, 95% CI 1·46–24·8). When CRT was categorized into 3 groups based on dose (i.e. no CRT, 18 Gy, and >24 Gy), similarly increased risks were observed for the moderate and high dose categories (data not shown). Age at ALL diagnosis >7 years (versus 3 years or younger, HR = 3·01, 95% CI 1·14–7·94) and inclusion in the more recent TCCSG L99-15/L04-1502 protocol (versus L84-11, HR = 8·15, 95% CI 1·03–64·7) were independently associated with an increased risk of secondary cancers. The same model, but replacing treatment protocol with the anticancer drugs (i.e. CPM, yes versus no; etoposide, yes versus no; high-dose methotrexate, yes versus no) showed an attenuated risk estimate for CPM (HR = 1·84, 95 CI 0·32–10·4), despite it being statistically significant in the unadjusted analysis (OR = 3·05, 95% CI 1·06–8·76).

Discussion

The risk of secondary cancers in childhood ALL survivors may be influenced by genetic predisposition, but growing evidence shows therapeutic regimen to be another major contributing factor. The risk of developing secondary cancers should be interpreted in the context of the survival

Table III. Cox-regression analysis evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

Intention to treat analysis group (n = 2807)	Patients with Secondary cancer	Patients without Secondary cancer	Crude HR (95%CI)	Adjusted HR (95%CI)	P-value
Protocol					
L84-11	12	476	Reference	Reference	
L89-12	7	392	1·00 (0·37–2·69)	1·35 (0·47–3·84)	0·576
L92-13	4	336	0·78 (0·24–2·56)	3·64 (0·45–29·1)	0·224
L95-14	4	584	0·56 (0·17–1·91)	4·47 (0·46–43·6)	0·198
L99-15/L04-1502	10	982	1·12 (0·42–3·01)	8·15 (1·03–64·7)	0·047
Risk classification					
Standard risk	7	1021	Reference	Reference	
Intermediate risk	20	956	3·42 (1·44–8·08)	2·70 (0·84–8·69)	0·096
High risk	10	771	2·67 (1·02–7·03)	1·01 (0·21–4·84)	0·992
Age at ALL diagnosis					
3 years or younger	8	986	Reference	Reference	
4–7 years	12	965	1·63 (0·67–3·98)	1·76 (0·71–4·40)	0·224
8 years or older	17	888	3·10 (1·34–7·21)	3·01 (1·14–7·94)	0·026
Gender: Male/Female	18/19	1530/1207	1·29 (0·68–2·46)	1·37 (0·71–2·62)	0·347
Attained age ≥20 years: No/Yes	20/17	2054/685	0·89 (0·42–1·90)	0·46 (0·19–1·12)	0·089
Cranial irradiation: No/Yes	8/29	1310/1445	2·57 (1·15–5·75)	6·02 (1·46–24·8)	0·013
Maintenance >1·5 years: No/Yes	15/22	1547/1209	1·16 (0·57–2·36)	3·19 (0·55–18·4)	0·194
Anticancer drugs					
Anthracycline: No/Yes	4/33	182/2574	1·32 (0·45–3·89)	N/A	N/A
Cyclophosphamide: No/Yes	4/33	448/2308	3·05 (1·06–8·76)	N/A	N/A
Etoposide: No/Yes	24/13	1910/846	1·30 (0·65–2·60)	N/A	N/A
High-dose Methotrexate: No/Yes	15/22	793/1963	0·77 (0·23–2·54)	N/A	N/A

ALL, acute lymphoblastic leukaemia; HR, hazard ratio; 95% CI, 95% confidence interval; N/A, not available.
Total number of patients may not equal 2807 for all variables due to missing data.

probability for a given treatment protocol, as low survival will result in fewer secondary cancers. Although the lifetime incidence of secondary cancers has not yet been defined, within the first 20 years of initial diagnosis of childhood ALL, previous studies conducted the U.S. and Europe have estimated it to be between 2% and 5%. To our knowledge, our study is the first conducted among an Asian population to report estimates of the cumulative incidence of secondary cancers in childhood ALL survivors. We found that the cumulative incidence of any secondary cancers in ALL survivors was 1·0% at 10 years and 2·4% at 20 years, respectively.

The previous reports on secondary cancers in childhood ALL survivors are summarized in Table IV. In 1991, the Children's Cancer Group (CCG) evaluated 9720 cases of ALL diagnosed since 1972 (Neglia *et al*, 1991) with a more recent update reported by Bhatia *et al*(2002) The CCG report showed a cumulative incidence of 1·3% at 10 years after ALL diagnosis, whereas the Berlin-Frankfurt-Munster (BFM) study (Loning *et al*, 2000) observed an overall cumulative incidence of secondary cancers at 15 years of 3·3% and 2·9% (95% CI: 1·6%–4·2%) among patients in first CR. In 1991, a Norwegian study found an overall cumulative incidence of 2·9% by 20 years after diagnosis in a group of 895 patients treated between 1958 and 1985 (Nygaard *et al*, 1991). In the St. Jude study reported by Hijiya *et al* (2007) a comparatively higher cumulative incidence of 4·2% at 15 years and 11% at 30 years was found. Our study of Japanese patients resulted in cumulative incidence and SIR estimates that are consistent with these results reported by the CCG, BFM, and Norwegian studies.

Previous reports from the CCSS and BCCSS (Mody *et al*, 2008; Reulen *et al*, 2011) calculated cumulative incidence and SIR estimates of secondary cancers within cohorts of childhood cancer patients that have survived at least 5 years. The distribution of secondary cancer types reported by those studies appeared to be different compared to ours and other prospective clinical studies (Table IV). As shown previously and in our study, most AML and MDS developed within 5 years after diagnosis of ALL. Thus, studying 5 year childhood cancer survivors probably influenced the comparatively fewer numbers of AML/MDS secondary cancers observed in the CCSS and BCCSS (Table IV).

Our results are also consistent with previous studies with respect to the median latency period by secondary cancer type (shortest for AML/MDS/NHL)(Loning *et al*, 2000; Bhatia *et al*, 2002; Hijiya *et al*, 2007) over-representation of females (Neglia *et al*, 2001; Bhatia *et al*, 2002; Meadows *et al*, 2009) in secondary AML/MDS, and CRT as a strong risk factor for secondary cancer development.(Neglia *et al*, 1991; Nygaard *et al*, 1991; Loning *et al*, 2000; Borgmann *et al*,

Table IV. Previous reports on the incidence of secondary cancers among survivors of childhood ALL.

Authors	Group	Total ALL patients (n)	Treatment Year	Follow-up, years Total person-years (P-Y)	Patients with secondary cancer (n)	Type of secondary cancer	Cumulative incidence	SIR (95%CI)
Neglia *et al* (1991)	CCG	9720	1972–88	4·7 (0·2–16) 43 446 P-Y	43	10 leukaemia/lymphoma, 24 brain tumours, 9 other tumours	0·3% (0·2–0·5) at 5 years 1·5% (1·1–2·1) at 10 years 2·5% (1·7–3·4) at 15 years	42/6·1 = 6·85
Bhatia *et al* (2002)	CCG	8831	1979–95	5·5 (0–16·1) 54 883 P-Y	70	14 AML/MDS, 6 NHL, 2 HL, 19 brain tumours, 4 sarcoma, 4 thyroid cancers, 4 parotid tumours, 4 other tumours	1·3% (0·8–1·5)at 10 years 2·1% (1·4–2·8) at 15 years	7·2 (5·5–9·1)
Nygaard *et al* (1991)	Norway (NOPHO)	895	1958–85	10·5 7·2 (4·3–26·5) 6295 P–Y	8 (6)	3 brain tumours, 2 basal cell carcinoma, 1 thyroid cancer, 2 sarcoma	2·9% (SE 1·4) at 20 years	5·9 (2·2–12·9)
Kimball Dalton *et al* (1998)	DFCI	1597	1972–95	7·6 (0–24·0)	13	3 leukaemia/lymphoma, 5 brain tumours, 5 other solid tumours	2·7% (0·7–4·7)	N/A
Loning *et al* (2000)	BFM	5006	1979–95	5·7 (1·5–18) 28 605 P-Y	52	16 AML, 1 CML, 6 lymphoma, 13 brain tumours, 3 thyroid cancers, 13 other solid tumours	0·5% (0·4–0·6) at 5 years 1·5% (1·3–1·9) at 10 years 3·3% (1·6–5·1) at 15 years	14·1 (11–18)
Hijiya *et al* (2007)	St. Jude	2169	1962–98	18·7 (2·4–41·3) 29 179 P-Y	123	45 AML, 2 CML, 10 MDS, 6 lymphoma, 48 brain tumours, 9 sarcoma, 48 other solid tumours	4·2% (SE 0·5) at 15 years 10·9% (SE 1·3) at 30 years	13·5 (11–17)
Schmiegelow *et al* (2009)	NOPHO	1614	1992–01	10·4 (50% range: 8·0–12·6)	20	8 AML, 8 MDS, 1 brain tumour, 1 oral cancer, 1 LPD after SCT, 1 thyroid cancer	1·6% (SE 0·4) at 12 years	N/A
Mody *et al* (2008)	CCSS	5760	1970–86	21·2 (5–35)	185 (199)	4 AML, 7 NHL, 106 brain tumours, 11 breast cancer, 16 thyroid cancers, 13 sarcomas, 9 skin cancer, 26 others	5·2% (4·3–6·1) at 25 years	5·0 (4·1–6·0)
Reulen *et al* (2011)	BCCSS	No. of leukaemia patients was not available Total 17 981	1940–91	24·3 (50% range: 17·9–32·4) 80 028 P-Y	115 all leukaemias (not limited ALL)	7 leukaemia, 3 lymphoma, 27 brain tumours, 17 thyroid cancers, 61 other solid tumours	N/A	4·3 (3·6–5·2)
This study	TCCSG	2807	1984–05	9·5 (0·2–27) 27 658 P-Y	37	11 AML,5 MDS, 2 lymphoma, 13 brain tumours, 6 other solid tumour	1·0% (0·7–1·4) at 10 years 1·4% (0·9–2·0) at 15 years 2·4% (1·5–3·7) at 20 years	9·3 (6·5–12·8)

CCG, Children's Cancer Group; NOPHO, Nordic Society for Paediatric Haematology and Oncology; DFCI, Dana-Farber Cancer Institute; BFM, Berlin-Frankfürt-Münster; St. Jude, St. Jude Children's Research Hospital, St.Jude; CCSS, Childhood Cancer Survivor Study; BCCSS, British Childhood Cancer Survivor Study; TCCSG, Tokyo Children's Cancer Study Group; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CML, chronic myeloid leukaemia; LPD, lymphoproliferative disease; SCT, stem cell transplantation; SE, standard error; SIR, standardized incidence ratio; 95%CI, 95% confidence interval; N/A, not available.

2008; Schmiegelow *et al*, 2009) Another important finding in the present study is that no marked difference was observed in cumulative incidence between the five TCCSG protocols, but the multivariate analysis adjusting for confounders including CRT resulted in a statistically significant increased risk of secondary cancers in patients treated with the recent protocol (Table III). Because of the relatively short follow-up duration for patients included in the recent protocol and potentially complex interplay with treatment, at this point we consider this finding preliminary and it will be followed-up in future studies. Despite considerable reduction in the use of CRT over time, particularly for the more recent treatment protocols, we observed no evidence of a reduction in incidence of secondary cancers among children with ALL (Fig 2D). One explanation may be that CRT is probably linked mainly to secondary brain tumours, which only comprise approximately a third of all the secondary cancers. Furthermore, examination of the data showed that secondary brain tumours were diagnosed in patients enrolled in the earlier treatment protocols, a time when CRT was still commonly administered. Secondary cancers diagnosed in patients enrolled in the more recent treatment protocols were predominantly haematological. Given that the latency for secondary brain tumours is generally longer than that of haematological cancers, it is possible that a longer follow-up period may be needed to observe the effects of the reduction in CRT use. Finally, considering the poor prognosis of secondary AML/MDS (Fig 3D), it is important to identify the associated factors and minimize the development of secondary haematological cancers.

Therapy-related secondary cancers have been identified in patients receiving radiotherapy, chemotherapy, or combined modality therapy for ALL. Our study identified CRT as a strong risk factor, which was also found in the BFM study. (Loning *et al*, 2000; Borgmann *et al*, 2008) The cumulative incidence of secondary cancer for the irradiated group continued to increase with time even after more than 15 years following ALL diagnosis, possibly suggesting a long-term effect of irradiation on the rates of secondary cancers (Fig 2C). Even among the patients treated with more recent non-irradiated protocol, it is currently unknown whether the cumulative risk will remain constant, or whether secondary cancers might arise after a longer latency period. Multi-agent chemotherapy as part of multimodality therapy for cancers has increased the difficulty of assessing which agents might play a causative role in the development of secondary cancers. Alkylating agents, and more recently DNA-topoisomerase II inhibitors, have been linked to the development of secondary AML and MDS.(Hawkins *et al*, 1992; Le Deley *et al*, 2003) In contrast to previous reports, we were not able to demonstrate a clear relationship between the anthracyclines, etoposide or methotrexate and the occurrence of secondary cancers or specific types of secondary cancers.(Relling *et al*, 1999) The crude HR of CPM showed an increased risk of secondary cancers, but adjustment for confounders in multivariate analyses resulted in an attenuated and non-statistically significant finding.

Lastly, we found that cumulative incidence of secondary cancers in patients remaining in first CR was significantly higher than the patients who experienced a relapse of their primary ALL, changed treatment regimen, were lost to follow-up or died during first CR unexpectedly (Fig 2B). This finding was unexpected as it could be hypothesized that, because relapsed patients usually receive additional therapeutic exposures, they may potentially be at a higher risk of developing of secondary cancers. Nevertheless, a few studies provide some supportive data for our observations, including Borgmann *et al* (2008) who reported that the cumulative incidence of secondary cancers was unexpectedly low (1·3% at 15 years) despite repeated exposure to intense frontline and relapse treatment using BFM ALL-REZ Study data. In the St. Jude study (Hijiya *et al*, 2007), secondary neoplasms were observed in 123 out of 2,169 (5·7%) patients with continued first CR and in 45 out of 879 patients (5·1%) with relapse. In contrast, however, Bhatia *et al* (2002) demonstrated that the 10-year cumulative incidence of second malignancy was 0·91% in the patients with continued first CR compared with 1·2% in the entire cohort. The interpretation of these inconsistent results is difficult. It could be partially influenced by differences in OS among the patients with continued first CR and patients with relapse across the various studies.

One strength of the current study is that treatment of patients according to TCCSG therapeutic protocols ensured uniform access to standard therapy, giving us the opportunity to explore risk factors associated with secondary cancers in this cohort. Secondly, the follow-up duration was relatively long compared to previous prospective clinical studies and allowed us to describe the incidence of secondary cancers among patients treated on contemporary therapeutic protocols.

The results of this study should be interpreted in the context of acknowledged limitations. One major limitation is that this study was smaller than some previous studies, such as the CCG, CCSS and BCCSS, which may have affected our statistical power for certain analyses. Although all the patients in our cohort were treated according to therapeutic protocols, we do not have detailed information regarding actual cumulative exposures doses after relapse, which potentially could have influenced the development of second cancers. To address this concern, we conducted a sensitivity analysis (per protocol analysis) that included only patients who had completed all planned treatment leading to first CR. These results were largely consistent with the primary analyses (Table S1). Also, we were unable to compare the clonal phenotypes and genotypes between the primary ALL in L84-11/L89-12 and certain secondary ALL candidates. The difficulty in distinguishing between the primary and secondary type of recurrence using current standard techniques is well-recognized. In both of these events, some clonal markers

are maintained between the original diagnosis and recurrence but others can be altered.(Szczepanski *et al*, 2001; Zuna *et al*, 2007) Thus, they were not included in the analysis.

In conclusion, we showed that cumulative incidence of secondary cancer after TCCSG-ALL therapy is relatively low (1·0% at 10 years and 2·4% at 20 years) compared to the previous reports, although it is still 9 times higher than in the general population. We confirm that CRT is a strong risk factor of secondary cancer, but we did not observe evidence for a decrease in incidence despite the marked reduction in CRT treatment in the more recent protocols. In view of the long latency periods and long life expectancy of ALL patients treated in childhood, long and careful follow-up of these patients is warranted. Efforts to identify the causative carcinogenic factors should continue, and future treatment protocols should take these factors into account to maximize the chances of a long and healthy life, while preserving the efficacy of ALL treatment.

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Authorship and Disclosures

Conception and design: Yasushi Ishida (YI) and Miho Maeda (MM); Financial support: YI and Akira Ohara (AO); Administrative support: MM, Masahiro Tuchida(MT) and AO; Provision of study patients: YI, MM, Chikako Kiyotani, Yuki Aoki, Yoko Kato, Shoko Goto, Sachi Sakaguchi, Kenichi Sugita, Mika Tokuyama (MT), Naoya Nakadate, Eizaburo Ishii, MT and AO; Collection and assembly of data: YI, MM and MT; Data analysis and YI, MM, and Kevin Urayama (KU); Data interpretation: YI, MM, MT and AO; Manuscript writing: YI and KU, Final approval of manuscript: All authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Schemas of the TCCSG (Tokyo Children's Cancer Study Group) protocols.

Fig. S2. Cumulative incidence of secondary cancers according to therapy of primary ALL.

Table S1. Cox- regression analysis limited to per protocol group evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

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ORIGINAL REPORT

Second Malignant Neoplasms After Treatment of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Purpose
Second malignant neoplasms (SMNs) after diagnosis of childhood acute lymphoblastic leukemia (ALL) are rare events.

Patients and Methods
We analyzed data on risk factors and outcomes of 642 children with SMNs occurring after treatment for ALL from 18 collaborative study groups between 1980 and 2007.

Results
Acute myeloid leukemia (AML; n = 186), myelodysplastic syndrome (MDS; n = 69), and nonmeningioma brain tumor (n = 116) were the most common types of SMNs and had the poorest outcome (5-year survival rate, 18.1% ± 2.9%, 31.1% ± 6.2%, and 18.3% ± 3.8%, respectively). Five-year survival estimates for AML were 11.2% ± 2.9% for 125 patients diagnosed before 2000 and 34.1% ± 6.3% for 61 patients diagnosed after 2000 ($P < .001$); 5-year survival estimates for MDS were 17.1% ± 6.4% (n = 36) and 48.2% ± 10.6% (n = 33; $P = .005$). Allogeneic stem-cell transplantation failed to improve outcome of secondary myeloid malignancies after adjusting for waiting time to transplantation. Five-year survival rates were above 90% for patients with meningioma, Hodgkin lymphoma, thyroid carcinoma, basal cell carcinoma, and parotid gland tumor, and 68.5% ± 6.4% for those with non-Hodgkin lymphoma. Eighty-nine percent of patients with brain tumors had received cranial irradiation. Solid tumors were associated with cyclophosphamide exposure, and myeloid malignancy was associated with topoisomerase II inhibitors and starting doses of methotrexate of at least 25 mg/m^2 per week and mercaptopurine of at least 75 mg/m^2 per day. Myeloid malignancies with monosomy 7/5q− were associated with high hyperdiploid ALL karyotypes, whereas 11q23/*MLL*-rearranged AML or MDS was associated with ALL harboring translocations of t(9;22), t(4;11), t(1;19), and t(12;21) ($P = .03$).

Conclusion
SMNs, except for brain tumors, AML, and MDS, have outcomes similar to their primary counterparts.

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INTRODUCTION

As many as one third of all deaths in childhood acute lymphoblastic leukemia (ALL) are caused by toxicities or second malignant neoplasms (SMNs).[1-4] Previously reported cumulative incidences of SMNs have varied from less than 1% to 10% or more because of differences in antileukemic therapy and in duration, accuracy, and completeness of follow-up.[1,2,5-18] Partly because of their rarity, little is known about the etiology of SMNs or about the treatment options that offer the best chances of cure.[1]

With the goal of improving overall survival in childhood ALL and providing guidelines for treatment, the international Ponte di Legno consortium of ALL study groups has studied uncommon subgroups of childhood ALL.[19-23] This is the largest study of SMNs after therapy for childhood ALL reported to date, and it presents new potential risk factors and provides survival rates for distinct subsets.

PATIENTS AND METHODS

Review of Patient Data

In the February 2010 issue of *Leukemia*, 16 cooperative study groups from Europe, North America, and Asia reported clinical outcomes, including the occurrence of SMNs, of 54,068 children and adolescents up to 21 years of age with newly diagnosed ALL enrolled onto controlled clinical trials between 1980 and 2007.[5-17,24-26] From these 16 groups as well as from FRALLE (French Acute Lymphoblastic Leukaemia Study Group) and the childhood leukemia branch of the European Organisation for Research and Treatment of Cancer (EORTC), we collected data on individuals with SMNs to form a common database with predefined variables comprising clinical and biologic data (including cytogenetic characteristics for myeloid neoplasias) as well as outcomes (Appendix Table A1, online only). Furthermore, we recorded clinical and biologic characteristics of their primary ALL as well as treatment given and status at latest follow-up. The data available for this study were retrieved from the groups' central ALL databases. If patient data on drug doses were unavailable, the patients were assigned the drugs and doses listed in the ALL protocols onto which they were enrolled. Accrual of data for patients with ALL who did not develop SMNs was not part of the study. The study was approved according to regional institutional review board requirements. All data were compiled at Rigshospitalet (Copenhagen, Denmark), and the database was approved by the Danish Data Protection Authorities.

Statistical Analysis

Differences in distribution of individual parameters among subsets were analyzed by using nonparametric tests.[27] Since accrual of data for patients with ALL who did not develop SMNs was not part of this study, odds ratios for SMNs in relation to specific exposures are not included. Instead, we analyzed patterns of ALL characteristics and therapy by subsets of SMNs to determine whether certain ALL subtypes or drug exposures were more prevalent within specific subsets of SMNs. Survival after an SMN was defined as time from diagnosis of the SMN to death as a result of any cause or to last follow-up. The Kaplan-Meier method was used to estimate survival rates with SEs calculated according to Greenwood.[28] Differences in survival rates were compared with the log-rank test.[29] The Cox proportional hazard model was used for selected analysis of survival after SMNs.[30] Two-sided *P* values below .05 were regarded as significant.

RESULTS

In all, 659 patients diagnosed with ALL between 1980 and 2007 were registered with a malignant neoplasm or a CNS tumor as the first event after diagnosis of ALL. Seventeen SMNs reported as ALL (n = 12), acute undifferentiated leukemia (n = 2), or myeloid malignancies with monosomy 7 (n = 1) or t(9;22)(q34;q11.2) (n = 2) at diagnosis of both ALL and the subsequent SMNs were excluded because the clonal relationship to the original leukemia could not be confidently verified, leaving a total of 642 study patients.

Table 1 reports clinical information on the 642 SMNs by subtype. The interval between diagnosis of ALL and occurrence of SMNs was significantly associated with the subtype of SMN, being shortest for hematologic malignancies and longest for carcinomas and meningiomas ($P < .001$; Fig 1 and Table 1). Thus, among the 48 SMNs diagnosed more than 15 years from the diagnosis of ALL, 35% were meningiomas (n = 15) or other CNS tumors (n = 2); 31% were non–skin carcinomas (n = 15), including six thyroid cancers; 15% were melanomas (n = 4) or other skin cancers (n = 3); and 17% were hematologic malignancies (n = 5); sarcomas (n = 2); or testicular cancer (n = 2). Eight patients with cancer-predisposing diseases are described in Appendix Table A2 (online only).

Patterns of SMNs by ALL-Presenting Features

Although distribution of sex, age, and WBC count at diagnosis of ALL varied significantly among the major categories of SMNs for the entire cohort (Table 1), this was not the case for the subset of 201 patients who were not irradiated and did not undergo hematopoietic stem-cell transplantation during first-line ALL treatment ($P > .45$ for all analyses; Appendix Table A3, online only).

Immunophenotype

Of the 186 patients with AML and 69 patients with myelodysplastic syndrome (MDS), the ALL lineage (B-cell precursor or T-cell lineage) was available for 217 patients. When analyzing only the 192 patients who did not receive irradiation and did not receive transplantation but who did have ALL immunophenotype available, the prevalence of T-cell ALL did not differ significantly among the categories of hematologic malignancies, CNS tumors, carcinomas, and other tumors (7.8%, 10.0%, and 16.7%, respectively; $P = .38$), but 26.6% of all patients with AML (42 of 158) and 8.5% of all patients with MDS (five of 59) initially had T-cell ALL. Patients with AML were overall more likely than those with other hematologic malignancies (n = 136) to have had T-cell ALL (26.6% *v* 13.2%; $P = .005$) with the same trend (10.0% *v* 5.6%; $P = .33$) in the subsets of patients who did not receive irradiation and did not receive transplantation. The interval between diagnosis of ALL and SMN was significantly shorter for the 11 patients who did not receive irradiation and did not receive transplantation but who had T-cell ALL than for the 130 patients with B-cell precursor ALL who had developed hematologic malignancies (median, 1.6 *v* 3.0 years; $P = .001$). Finally, 91% (10 of 11) of the patients who developed Langerhans cell histiocytosis had T-cell ALL compared with 20.4% among the other SMNs ($P < .001$).

Karyotype and Therapy-Related Myeloid Neoplasias

The time to develop AML was shorter than the time to develop MDS (median, 2.7 *v* 3.3 years; $P = .01$), reflecting a higher proportion of 11q23/*MLL* rearrangements with short latency (median, 2.5 years) in patients with AML (58% *v* 5% of patients with MDS with an aberrant karyotype; $P < .001$). By contrast, treatment-related myeloid neoplasia (t-MN; ie, AML or MDS) with monosomy 7 (median interval, 3.7 years) occurred in 22% of patients with AML and in 50% of patients with MDS with an aberrant karyotype ($P = .002$).

Among the 44 patients with t-MN with monosomy 7, 5q−, or 11q23/*MLL* rearrangements (one t-MN with both monosomy 7 and 11q23/*MLL* rearrangements was excluded) and an available karyotype for the ALL clone, the cytogenetic aberrations of their ALL and t-MN were highly correlated. Thus, among the 25 patients who developed 11q23/*MLL*-rearranged t-MN, 13 had ALL with classical recurrent translocations—t(9;22)(q34;q11.2) (n = 1), t(1;19)(q23;p13.3) (n = 2), t(12;21)(p13;q22) (n = 8), or 11q23/*MLL* rearrangements (n = 2 [different 11q23/*MLL* rearrangement in the two clones]—and six had a high hyperdiploid ALL karyotype (modal chromosome number above 50), and six had other structural and/or numeric aberrations. In contrast, among the 19 patients who developed t-MN with 5q− or monosomy 7, 10 had a high hyperdiploid ALL karyotype, three had ALL clones with one of the above-listed classical translocations, and six had other aberrations ($P = .03$ by likelihood-ratio χ^2 test).

Patterns of SMNs by ALL Therapy

The pattern of SMNs was significantly influenced by the preceding ALL therapy (Table 2). The 12 patients with CNS tumors who had not received CNS irradiation were diagnosed at significantly shorter intervals after ALL than the 97 patients with CNS tumors that occurred after CNS irradiation (median, 6.6 *v* 9.1 years; $P = .01$).