質問２５．現在、通院をしていますか？

１．はい　　２．いいえ
「はい」の場合は質問２６へお進みください。
「いいえ」の場合は質問３３へお願いします。

質問２６．質問２５で「はい」（通院している）と答えた方はどの診療科を受診していますか。
（複数回答可能）

１．小児科　　２．内科　　３．外科　　４．呼吸器科　　５．循環器科
６．消化器科　７．泌尿器科　８．産婦人科　９．皮膚科　　１０．整形外科
１１．脳神経外科　　１２．耳鼻科　　１３．精神科　　１４．心療内科
１５．その他（　　）

質問２７．質問２５で「はい」（通院している）と答えた方は以下のどの理由ですか？

１．初発小児がんの定期検診（病院名：　　）
（回数：　　／年）

２．晩期合併症の定期検診　（病院名：　　）
（回数：　　／年）

３．晩期合併症の継続診療　（病院名：　　）
（回数：　　／年）

質問２８．通院されている病院は以下のいずれですか？
（複数回答可能）

１．治療を受けた病院　　２．それ以外の病院（受診病院の数は？　　）

「それ以外の病院」の場合は質問２９へお進み下さい。

質問２９．質問２８の「それ以外の病院」は以下のうちどれに当てはまりますか。
（複数回答可能）

１．がん専門病院　　２．地域の総合病院　　３．地域の小さな病院や診療所

質問３０．定期的に通院する病院を変えたことはありますか？

１．はい　　２．いいえ
「はい」の場合は以下の質問３２と質問３３にお答えください。

質問３１．病院を変えた時期を教えてください。
（複数回答可能）

①（　　）歳頃
②（　　）歳頃
③（　　）歳頃
④（　　）歳頃
①

質問３２．病院を変えた理由を教えてください。
（複数回答可能）

１．主治医の転勤　　２．ご自身の転居　　３．通っていた病院に行きづらくなったから
４．もっと良い病院を見つけたから

質問３３．公費医療助成制度（小児慢性特定疾患治療研究事業、身体障害者手帳など）は
いつまで利用していましたか？

１．わからない　　２．利用していた　（　　）歳まで
３．今でも利用している（制度名：　　）
４．利用していない

質問３４．現在の医療費は月額どれくらいかかっていますか？

１．かかっていない　　２．（　　）円ぐらいかかっている　　３．わからない

質問３５．　質問３４の「２」に回答した方への質問ですが、支払いはどなたがされていますか。

１．ご自身　　２．親　　３．その他（　　）

質問３６．ご自身の健康管理について、どの程度行っていますか？

１．十分気を付けている　２．ある程度は気を付けている　３．時々気を付けている
４．特に気を付けていない　５．その他（　　）

【就労のことを教えてください】

質問３７．就労について現在の状況を教えてください。

１．学生　　２．正社員として就職　　３．正社員ではないが就職　　４．就労した経験がある
５．就労した経験がない（理由　　）

＊質問３８から質問４１は、就労経験のある方へお聞きします。

質問３８.採用面接のときに会社の人へ病気のことを伝えましたか？

１．はい　　２．いいえ

質問３９．質問３８で伝えたか、伝えなかったかにかかわらず不都合なことがありましたか？

１．あった　　２．なかった

「あった」と答えた方は具体的にお書きください。

質問４０．　採用後に会社の人へ病気のことを伝えましたか？

１．はい　　２．いいえ

質問４１．質問４０で伝えたか、伝えなかったかにかかわらず不都合なことがありましたか？

１．あった　　２．なかった

「あった」と答えた方は具体的にお書きください。

【皆様にお聞きします】

質問４２．下記の言葉の中で理解している（人に説明できる程度）と思う言葉に○をつけてください。

１．治癒　　２．寛解　　３．晩期合併症　　４．長期フォローアップ（長期支援）

５．ＡＹＡ（アヤ世代）　５．小児がん拠点病院　　６．相談支援センター

質問４３．治療した病院などが、治療が終了した後も長期にわたってあなたの健康状態について追跡調査をすることはどのように思われますか？

１．　大変良いことだ
２．　よいことだとは思うが、そっとしておいてほしい気持ちもある
３．　調査結果を教えてもらえるのであれば協力してもよい
４．　何か問題があれば病院を受診するので必要はない
５．　その他　（　　）

質問４４．今後、小児がんに関係することで困ったことがあった時に相談する人は誰ですか？（複数回答可能）

１．家族　　２．友人　　３．元主治医　　４．現在の担当医
５．小児がん拠点病院の相談員　　６．その他（　　）

質問４５．小児がん拠点病院の相談支援センターを利用したいと思いますか？

１．思う　　２．そうは思わない　　３．わからない

それはどのような理由からですか？

【その他】

アンケートにある質問以外で何か困ったことはありますか？

どのようなことでも結構ですので、ご自由にご意見をお書きください。

以上でアンケートを終わります。
ご協力ありがとうございました。
平成　　年　　月

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Ⅲ.研究成果の刊行に関する一覧表

III. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
該当なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
清谷知賀子、 松本公一	[長期予後と成人後の医学的問題]小児がん	日本医師会雑誌	143(10)	2130-4	2014
Yasushi Ishida, Miho Maeda, Kevin Y Urayama, Chikako Kiyotani, Yuki Aoki, Yoko,Kato, shoko Goto, Sachi Sakaguti, Kenichi Sugita, Mika Tokuyama, Hisaya Nakadate, Eizaburo Ishii, Masahiro Tsuchida, Akira Ohara.	Secondary cancers among children with acute lymphoblastic leukaemia treated by the Tokyo Children's Cancer Study Group protocols: a retrospective cohort study.	Br J Haematol	164	101-112	2014

Ⅳ．研究成果の刊行物・別刷

小児がん長期予後と成人後の医学的問題

小児がん

清谷知賀子*　松本公一**

キーワード●晩期合併症，長期フォローアップ，治療サマリー，小児がん拠点病院

はじめに

治療技術の進歩により小児がんの長期生存率は70～80%に及び，初期の小児がん経験者（childhood cancer survivor；CCS）世代は40歳代に達している．米国では成人の1,000人に1人がCCSと言われ，わが国でもCCSの成人人口は着実に増加している．

多くのCCSは，日常的には大きな問題なく過ごすことができるが，米国のCCS研究[1]などで明らかにされたように，成人となったCCSの中には，若年成人のうちから少なからぬ慢性健康障害が認められる．がん治癒と考えられる小児がん5年生存者を対象にした調査でも，小児がん診断から30年経過すると慢性健康障害による死亡例が多い[2]．

小児がん長期予後の改善と共に，CCSの健康管理という新たな課題への対応が必要になっている．

1 小児がん晩期合併症と長期フォローアップ

腫瘍診断から5年以上経過後に発生ないし腫瘍診断から5年以上継続する，疾患や治療に関連する合併症を晩期合併症と言う．小児がん晩期合併症には，疾患や治療時年齢，手術，使用した抗がん剤の種類や総投与量，放射線治療の照射野や線量など，多くの因子が関与し，またその合併症は心臓，内分泌，腎泌尿器，筋骨格系・皮膚，歯牙，神経・認知機能，性腺機能・不妊，二次がん[3]（表1）など多岐にわたり，身体的・社会的に生涯の支援が必要な場合もある．

晩期合併症は小児期に発症するとは限らず，内分泌障害のように小児期から成人後まで継続的治療管理が必要なものもあれば，循環器系合併症，脳血管系合併症，高血圧，脂質・糖代謝異常などのように，若年成人に発症する可能性を踏まえて予防的対応・健康管理を要するものもある．慢性健康障害は加齢により影響が増すが，壮年期以後の問題は，米国のCCSコホートも1970年以後の診断例であり，現時点ではまだほとんど情報がない．

もしCCSに晩期合併症情報が伝えられず，適切な長期フォローアップ（以下，FU）が行われなければ，社会の前線に立つ成人期に突然健康破綻を生じて，生命を脅かす場面や仕事や家庭に大きな影響を与える場面に遭遇してしまうかもしれない．たとえばアントラサイクリン系抗がん剤による蓄積性心毒性は，激しい運動や妊娠出産などの負荷により，治療終了から10年以上経過してから突然心不全を発症することがある[4]．CCSにリスク情報を還元し，晩期合併症の予防や早期介入を行えれば，これらの影響を最小限にできる可能性がある．

The long-term follow-up for survivors of childhood cancer

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表1　小児がん晩期合併症

臓器・機能	代表的なリスク因子	主な晩期合併症
内分泌	原疾患 アルキル化剤 放射線治療	成長ホルモン分泌不全・低身長 甲状腺機能低下症，副腎機能低下症 二次性徴障害・性腺機能障害・不妊症 代謝異常・肥満，尿崩症
心臓	アントラサイクリン系抗がん剤 放射線治療	心筋障害・心拡大・心不全 心膜炎，不整脈，心筋梗塞，突然死
肺	ブスルファン ブレオマイシン 放射線治療	肺線維症・肺活量低下 低酸素血症・呼吸困難
腎臓	プラチナ製剤 イホスファミド 免疫抑制薬（FK506, CyA） 放射線治療 手術	腎機能低下・腎不全 腎血管性高血圧 尿細管機能障害 タンパク尿・血尿・尿糖
消化管	手術・放射線治療 GVHD	下痢・イレウス 食欲不振，栄養障害
中枢神経系	原疾患・手術 放射線治療 大量メトトレキサート・髄注	認知機能障害 白質脳症
視機能	原疾患，GVHD 放射線治療・ステロイド	視力・視野障害，結膜炎・涙液分泌低下 白内障・緑内障
聴覚	原疾患・放射線治療 プラチナ製剤	聴力障害（プラチナ製剤では高音域聴力障害），耳鳴
歯牙	ブスルファン 放射線治療 年齢	形成不全，矮小歯，歯根形成異常， 萌出遅延，う蝕，唾液腺障害，歯肉炎， 顎骨発育障害
筋骨格系・皮膚	ステロイド 手術・放射線治療 GVHD	大腿骨頭壊死 骨格変形，骨成長障害 皮疹・皮膚乾燥・白斑・関節異常
二次がん	放射線治療 エトポシド・アルキル化剤 遺伝的素因	脳腫瘍，血液腫瘍，固形腫瘍
心理社会的問題	すべて	学習障害，PTSD・こころの問題，自立障害，進学・就労困難，結婚の問題

代表的な小児がん晩期合併症を臓器・機能別に，代表的なリスク因子と共に示したが，実際には疾患部位，抗がん剤投与量，放射線治療の線量や照射範囲，併用治療などさまざまな要素が関与するため，実際の診療情報に基づいて晩期合併症リスクを判断する必要がある．

欧米では巨額の予算を投入して，ライフサポートとしての長期FU体制を組み，診断治療情報と晩期合併症を含む臨床情報を大規模に集積すると同時に，DNAサンプルの収集も行って，遺伝学的情報を含めたリスク因子の解析を進めている．

II 小児がん治療情報（治療サマリー）とリスク別フォローアップ

小児がんは血液腫瘍・固形腫瘍・脳腫瘍までを含む希少疾患の集合であり，それぞれで化学療法，手術，放射線，造血幹細胞移植を組み合わせた多様な集学的治療が行われている．同一疾患でも，発症時年齢により疾患バイオロジーが異なり予後や治療が大きく変わる場合や，臓器や神経・認知機能の未熟性への配慮で年齢により異なる治療戦略をとる場合，また時代背景により治療法が違う場合などがあるため，小児がん長期FUには経験者個別の治療情報の把握が欠かせない．

幼少期に治療を受けた患者は疾患・治療を把握していないことがあるが，年月が経ってから遠い過去の診療情報を入手することはきわめて難しい．そのため現在小児がん治療施設では，CCS自身が疾患・治療内容を把握し，晩期合併症リスクを認識して，能動的に自己の健康管理ができるように，患者の「治療サマリー」を作成して患者・家族に渡す動きが広がっている．現在，わが国で施設を越えて使用されているのは，患者管理による診療情報ツールである，日本小児白血病リンパ腫研究グループ（Japanese Pediatric Leukemia/Lymphoma Study Group；JPLSG）長期FU委員会作成の治療サマリーのフォーマット（図1）

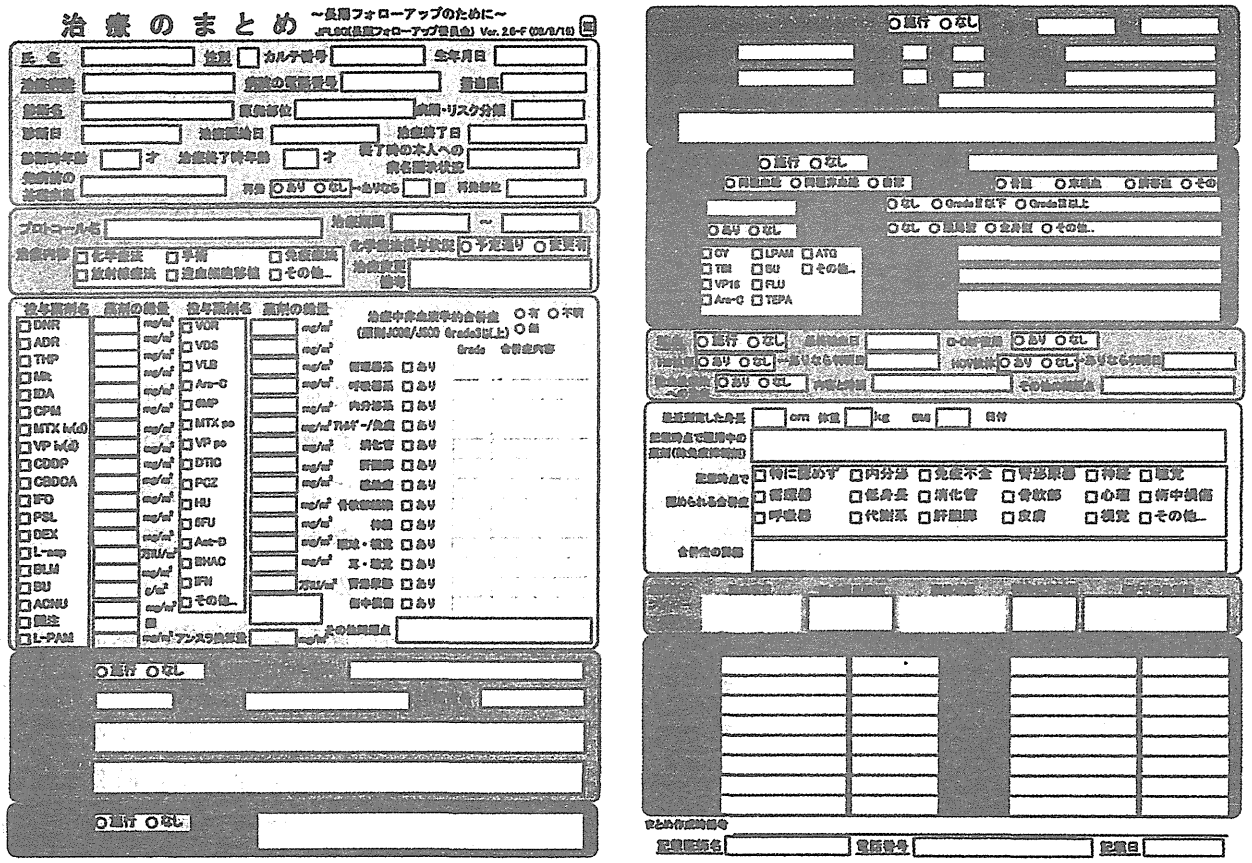

図1　JPLSG 治療サマリー

JPLSG 長期フォローアップ委員会作成の患者管理型診療情報ツール「治療のまとめ」．各治療施設で，診断，治療プロトコール，抗がん剤総投与量，手術，放射線治療，造血幹細胞移植などの情報が記入され，患者家族に配付されている．

のみであり，小児腫瘍医を中心に利用されている．

同委員会では長期 FU の指針として，さまざまなリスク因子をまとめた 5 段階の FU レベルも推奨している（表2）．リスク因子の詳細は長期 FU の参考資料[5,6]に記載されているが，たとえばアントラサイクリン系抗がん剤による心筋障害は累積投与量依存性のため，ドキソルビシン換算総投与量 250mg/m² 以上で FU レベルが上がり，頭蓋照射も線量によって FU レベルが違う．内分泌合併症については日本小児内分泌学会のガイドライン[7]に詳しく示されている．

欧米では国ごとに異なる長期 FU ガイドラインを標準化するため，国際ハーモナイゼーション会議[8]を開催し，さまざまな項目について順次，各国のガイドラインの比較分析ならびに文献検索とエビデンスレベル設定を行い，検診の対象者，対象年齢，頻度，検診方法などの検討を進めている．まず，胸部照射による乳がんの検診ガイドライン[9]が 2013 年の *Lancet Oncology* 誌に掲載された．その中では，胸部照射 20Gy 以上の場合は，マンモグラフィないし MRI による毎年の検診を，25 歳以上ないし照射後 8 年のいずれか遅いほうで開始することが強く推奨されている．心筋症検診のガイドラインも近く同誌に掲載予定であり，現在は性腺機能障害・不妊症について準備が進められている．

III 小児がん経験者のトランジション

小児がん長期 FU を担当医や小児がん診療施設のみで担うことは事実上不可能であり，小児から成人へ，地域や診療部門の枠組みを超えた連携・移行（トランジション）が必要になる．日本小児科学会では小児がんのような長期的視

表2　FUレベル

レベル	分類	対象者	ケア提供者	頻度	評価内容
1	一般的健康管理群	・外科手術のみ（頭頸部・胸腹部・四肢）	健康診断医/家庭医	年1回	・一般診察 ・一側臓器摘出後の場合，当該臓器の機能評価 ・予後調査が望ましい
2	経過観察群	・低リスク化学療法を受けた患者（DOX 250mg/m²未満かつCY 5g/m²未満かつCDDP 300mg/m²未満かつIFO 45g/m²未満かつDex使用歴なし）	家庭医または長期FU外来	年1回	・一般診察 ・治療関連晩期合併症が疑われる場合，必要な検査を行う ・予後調査が望ましい
3	標準的FU群	・高リスク化学療法を受けた患者（DOX 250mg/m²以上，CY 5g/m²以上，CDDP 300mg/m²以上，IFO 45g/m²以上，Dex使用歴あり） ・自家移植併用大量化学療法（放射線照射含まず）を受けた患者 ・20Gy未満全脳放射線照射を受けた患者 ・全脳以外の放射線照射を受けた患者	長期FU外来	年1回	・一般診察 ・治療関連晩期合併症に対する検査を行う ・成人期以後もFU継続が望ましい
4	強化FU群	・20Gy以上全脳放射線照射を受けた患者 ・同種造血細胞移植を受けた患者 ・再発治療患者 ・遺伝性腫瘍症候群のある患者 ・脳腫瘍患者 ・自家血液細胞移植併用大量化学療法（放射線照射含む）を受けた患者	長期FU外来	年1回	・一般診察 ・治療関連晩期合併症に対する検査を行う ・成人期以後もFUが必要
5A	要介入群（重篤な病態・全身的問題）	・臓器機能障害による社会参加不能患者 ・臓器機能低下に伴う要生活制限患者 ・晩期合併症症状のある患者 ・晩期合併症に対して治療が必要な患者	長期FU外来	3～6か月に1回	・一般診察 ・治療関連晩期合併症に対する検査および治療 ・成人期以後もFUが必要
5B	要介入群（疾患特異的な問題）	・臓器特異的な外科的治療後のフォローが必要な患者（例：骨肉腫治療後の人工関節，網膜芽腫治療後の義眼）	専門診療科外来	必要時	・専門診療科でのFUが必要

DOX；ドキソルビシン，CY；シクロホスファミド，CDDP；シスプラチン，IFO；イホスファミド，Dex；デキサメタゾン
治療終了後5年以上経過したCCSを対象とした，治療内容の総合的評価によるFU強度の簡易指標．晩期合併症の内容とリスクに基づいて，FUの対象者，ケア提供者，頻度，評価内容の概略を示しているが，個別の薬剤投与量に対応した基準ではなく，複合的作用や併用療法の合併症も本基準では評価できないことに注意を要する．
（JPLSG長期フォローアップ委員会長期フォローアップガイドライン作成ワーキンググループ編：小児がん治療後の長期フォローアップガイドライン．医薬ジャーナル社，大阪，2013；15-16より引用，改変）

野が必要な疾患に対し，「小児期発症疾患を有する患者の移行期医療に関する提言」を取りまとめた．がん経験者の健康管理は成人領域でも端緒に就いたところであるが，CCSが安心して自立した社会生活を送れるようにするためには，プライマリケア医や専門医/施設とのより良い連携を模索し，小児がん領域に適した移行期医療を構築する必要がある．

移行期医療モデルとして，プライマリケア医に長期FUを依存するモデルでは，組織化されたトランジション，治療サマリー，サバイバーケアプラン，プライマリケア医の教育，FUガイドラインなどの整備が必要で，多忙なプライマリケア医では十分に把握することが困難なうえ，CCS自身にも自立と健康管理責任が求められ，FUロスにもつながりやすいと考えられる．

そのため長期FUセンターや治療施設が司令塔として患者の治療情報やリスクを把握し，プライマリケア医と密接に連携して，必要な指示や情報発信を行うセンター方式ないし共同方式モデルがより望ましい[10]と考えられている．

EU諸国ではeHealthを視野に入れて，患者の臨床研究登録時の情報が自動入力され，長期FUガイドラインを組み込んで個別の推奨長期FUガイドが表示される「サバイバー・パスポート」のネットベースでの運用を開始した．

本邦では小児がん診療と患者家族支援のために，2013年に全国15施設の小児がん拠点病院が指定され，集約的な小児がん診療，患者・家族支援，難治小児がん対策，患者の自立支援などを含めた長期FU体制の整備，小児がん登録の整備などを開始したところである．今後はプライマリケア医を含めた組織化が必須であり，プライマリケア医・専門医に必要な情報が正確に迅速に共有化できる体制を構築する必要がある．小児がん治療施設とプライマリケア医・専門診療施設をつなぐ長期FUセンターの設立が望まれる．

おわりに

CCSが成人受診者に占める割合は今後ますます高まり，日常診療上の留意点の1つとなることが予想される．CCSの成人後の医学的問題に対するシームレスな取り組みは，CCSのwell-beingのためだけでなく，社会的・経済的に重要な課題の1つであると考えられる．

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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

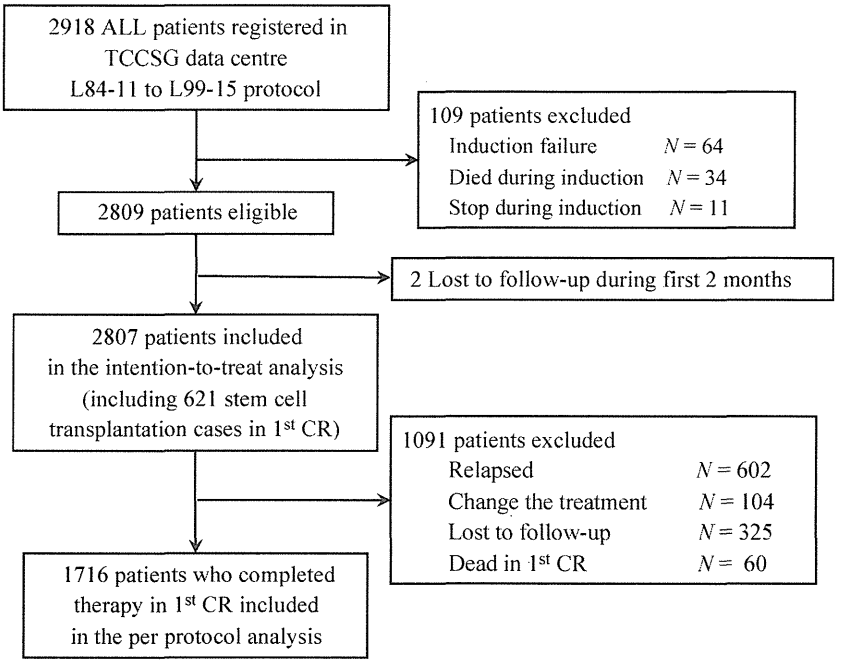

Fig 1. Flow diagram describing the criteria for patient selection. Total of 2918 newly diagnosed children with ALL aged 1–15 years entered into 5 consecutive Tokyo Children's Cancer Study Group (TCCSG) studies (L84-11, L89-12, L92-13, L95-14 and L99-15/L04-1502. The current analysis is primarily based 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/m^2)						CPM (mg/m^2)	VP-16 (mg/m^2)	IV MTX (g/m^2)	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.

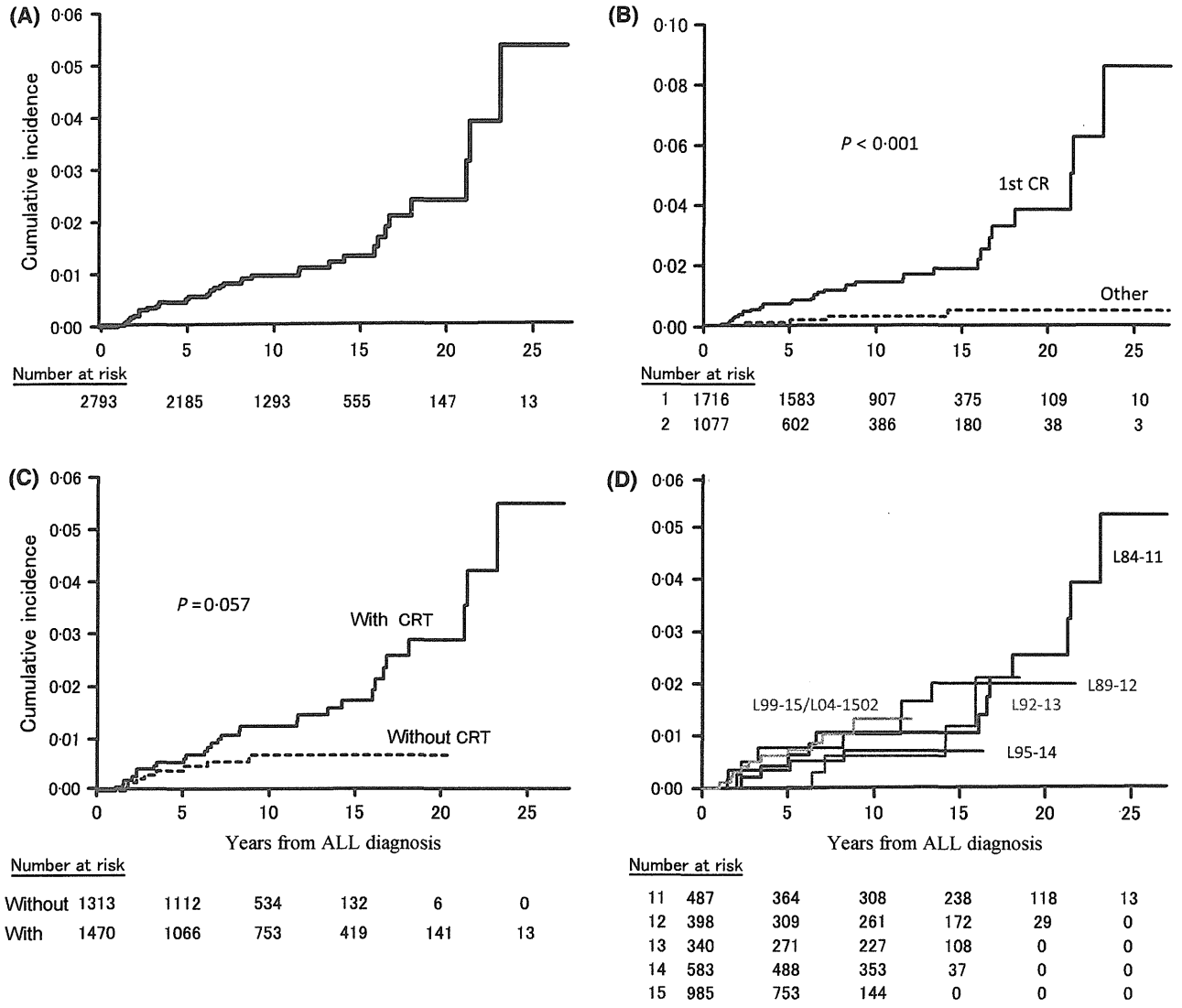

Fig 2. Cumulative incidence of secondary cancers. Shown are the cumulative incidences of secondary cancers as a function of time since primary ALL diagnosis over a maximum follow-up of 27 years. (A) Overall cumulative incidence of secondary cancer among the total patient cohort. (B) Overall cumulative 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 ($P = 0{\cdot}045$ 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,

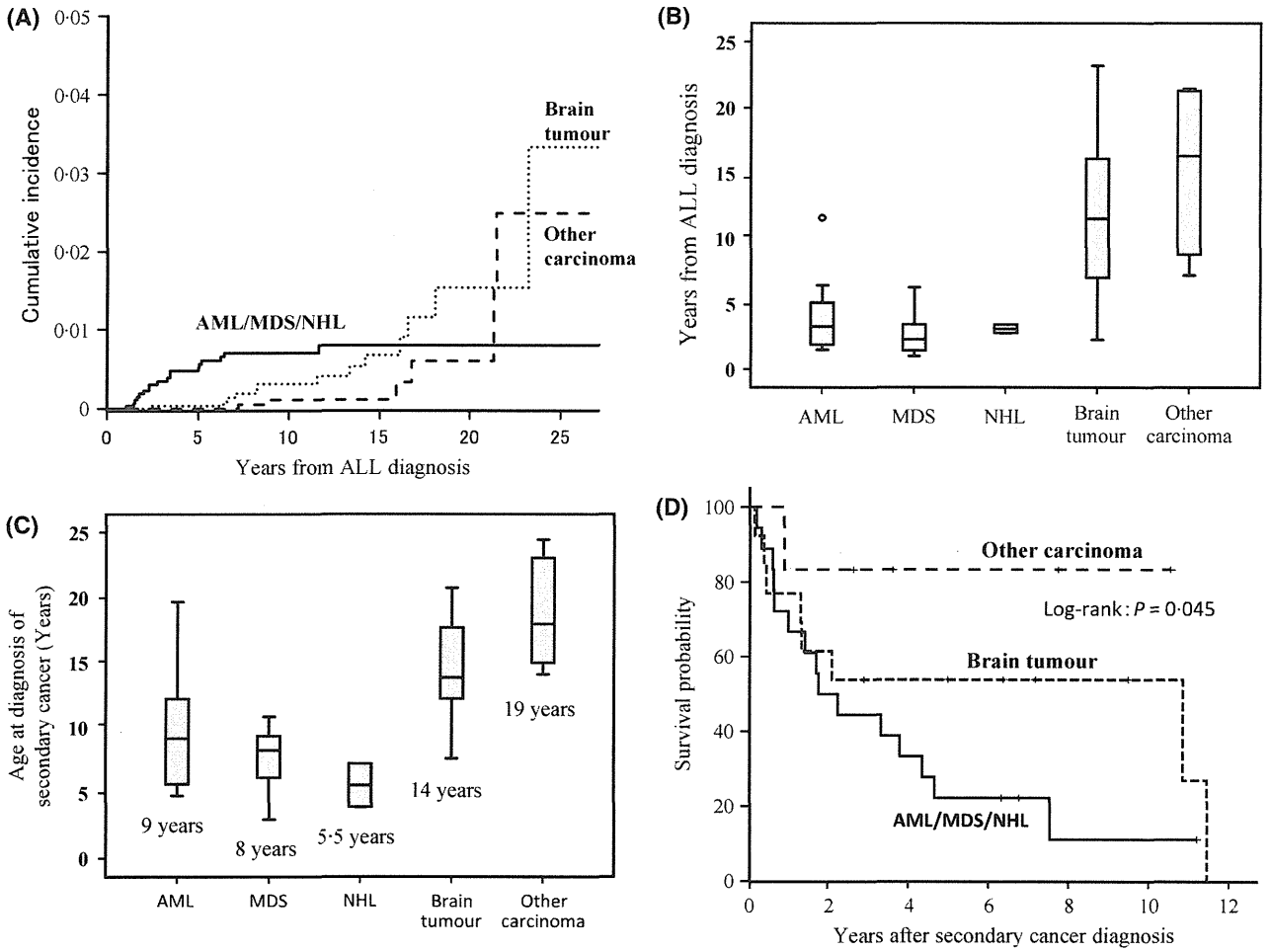

Fig 3. Clinical characteristics according to types of secondary cancer. (A) Cumulative incidence by years since ALL diagnosis of specific secondary cancers including AML/MDS/NHL (solid line), brain tumour (dotted line), and other carcinoma (dashed line). (B) The median latency period from diagnosis of 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*,