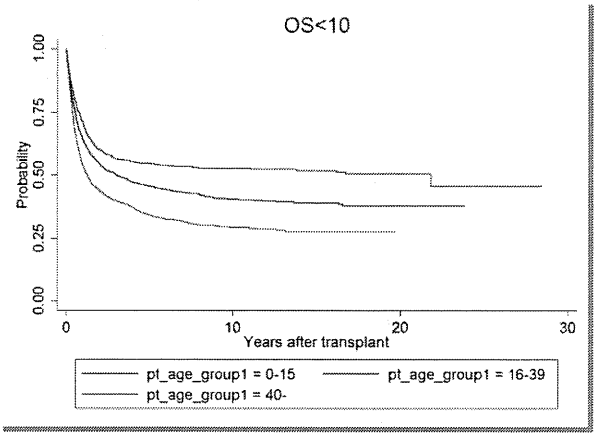
②Kaplan-Meier 曲線を描きます。

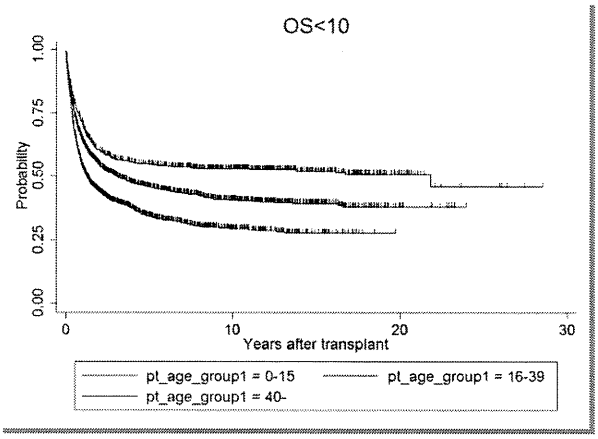
**sts graph if** (条件), **by**(群分けグループ変数) title(グラフのタイトル) ytitle(y 軸のタイトル) xtitle(x 軸のタイトル)
オプション

様々な設定でのサブグループで抽出する際には、by( )グループ変数名を入力します。

例：AML、血縁移植で年齢別の解析
*sts graph if diagnosis==1 & t_cd>=2 & t_cd<=3, by(pt_age_group1) title(OS<10) ytitle(Probability) xtitle(Years after transplant)*




打ち切りイベントが発生した時点に縦線をつける場合には、オプション箇所に censored(single)を加えます。
*sts graph if diagnosis==1 & t_cd>=2 & t_cd<=3, by(pt_age_group1) censored(single) title(OS<10) ytitle(Probability) xtitle(Years after transplant)*




③グラフの保存

**translate @Graph** (グラフ名).emf, trans(Graph2emf)

graph 名にはスペース、<,>等は使用できません
emf の形式にてデータ(.dta ファイル)保存先のフォルダに保存されます

④生存解析結果を表示
個々のエンドポイントまたは打ち切りポイントにおける surival function，standard error，95%CI を表示することができます。

**sts list**,**by**(グループ変数) **at** (時間時点リスト)

例：*sts list if diagnosis==1 & t_cd>=2 & t_cd<=3, by(pt_age_group1) at(1 3 5)*

この例の場合は、エンドポイントまたは打ち切り観察時間１年、３年、５年時点での生存関数の結果を示します。

コマンドを実行すると下記の結果が表示されます。

```
failure _d:  event_os == 1
analysis time _t:  1year
```

| Time | Beg. Total | Fail | Survivor Function | Std. Error | [95% Conf. | Int.] |
|---|---|---|---|---|---|---|
| 0-15 | | | | | | |
| 1 | 670 | 274 | 0.7118 | 0.0147 | 0.6819 | 0.7395 |
| 3 | 485 | 134 | 0.5644 | 0.0163 | 0.5319 | 0.5956 |
| 5 | 429 | 14 | 0.5475 | 0.0164 | 0.5147 | 0.5790 |
| 16-39 | | | | | | |
| 1 | 1280 | 736 | 0.6432 | 0.0106 | 0.6221 | 0.6635 |
| 3 | 837 | 264 | 0.5017 | 0.0113 | 0.4794 | 0.5236 |
| 5 | 636 | 71 | 0.4565 | 0.0115 | 0.4338 | 0.4788 |
| 40- | | | | | | |
| 1 | 1055 | 948 | 0.5401 | 0.0110 | 0.5183 | 0.5614 |
| 3 | 591 | 254 | 0.3960 | 0.0112 | 0.3739 | 0.4179 |
| 5 | 378 | 70 | 0.3420 | 0.0114 | 0.3197 | 0.3644 |

左から１列目の time は、エンドポインもしくは打ち切りを観察した時間を示します。
２列目の Beg.total は、ある時点の開始時の観察者の人数を示します。
３列目の Fail は、この期間に観察された failure の数を示します。
４列目は Survival Function(生存率)を示します。
５列目は Standard Error を示します。
6-7 列目は 95%CI を示します。

at(時間時点リスト)のオプションをつけずに実行すると、打ち切りまたはイベントが生じたエンドポイント(この例の場合は死亡)のすべての時点での生存率を計算します。

⑤生存解析における検定

1.Log-rank 検定

**sts test** グループ変数,オプション

オプションで設定変更を行わない限り Log-rank 検定を行います。
Wilcoxon 検定を行う場合には、オプションで指定してください。

2.Wilcoxon 検定

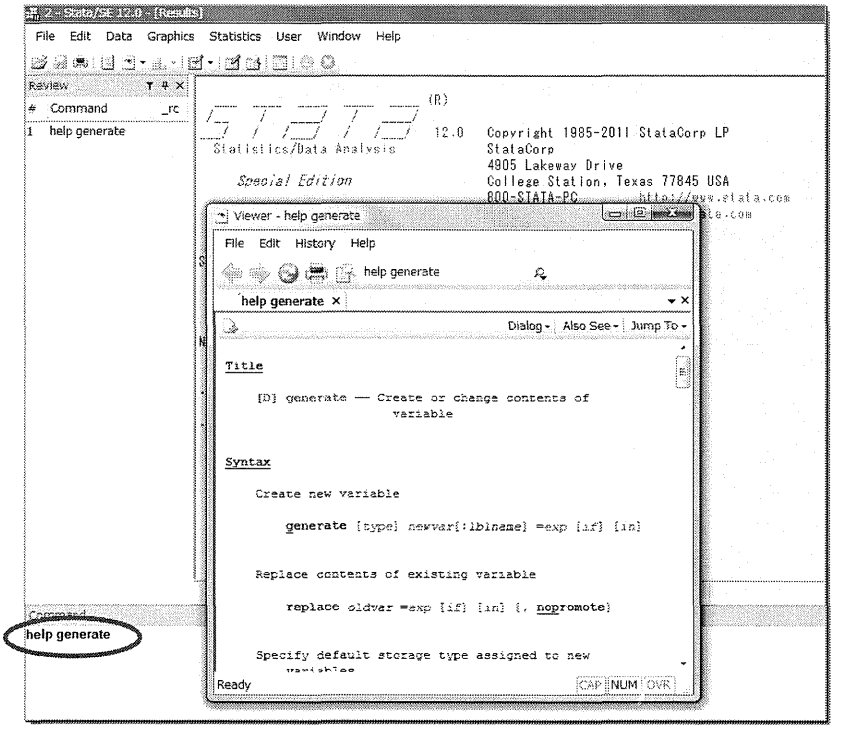
**sts test** グループ変数,wilcoxon

# ヘルプの使い方

## 1.コマンドについて調べる

①コマンドウインドウに調べたいコマンドを入力する。

**help 探すコマンド**
**search 探すコマンド　または キーワード**




マニュアル作成
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# 4. ワーキンググループ登録研究公表（学会発表、論文）一覧

| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 1-1 | 小児AMLにおける第2寛解期再移植例の成績と再移植の意義 | 多賀崇 | JSH2012 | |
| 1-2 | 非寛解期小児AMLにおける移植成績 | 岡本康裕 | JSHCT2012 | |
| 1-3 | ダウン症候群に合併した急性骨髄性白血病に対する造血幹細胞移植の成績 | 村松秀城 | JSPHO2011 | Pediatr Blood Cancer .( in press) |
| 1-4 | 小児AMLに対する自家移植の解析 | 坂口大俊 | JSHCT2012 | |
| 1-5 | 小児・思春期AML第一，第二寛解期に対するアロ造血幹細胞移植前処置の影響 | 石田宏之 | JSHCT2012 | |
| 1-7 | t(8;21)およびinv(16)異常を有する小児急性骨髄性白血病に対する造血幹細胞移植の成績 | 村松秀城 | JSHCT2013 | |
| 2-1 | AML患者に対するRISTの有用性に関する研究-骨髄移植と末梢血幹細胞移植の比較- | 金森平和 | ASH 2012 | |
| 2-3 | 成人AMLに対してiv Busulfanを用いた移植前治療による自家造血幹細胞移植の治療成績 | 山下卓也 | JSHCT2013 | |
| 2-4 | 成人AMLに対してiv Busulfanを用いた移植前治療による同種造血幹細胞移植の治療成績 | 山下卓也 | JSH2012 ,他 | |
| 2-5 | 初回寛解導入不応・再発非寛解期の急性骨髄性白血病に対する同種移植の予後解析 | 横山洋紀 | JSH2012 | |
| 2-6 | 各染色体分類における急性骨髄性白血病に対する同種移植の予後の比較 | 横山洋紀 | JSHCT2012 | |
| 2-7 | 急性骨髄性白血病に対する同種造血幹細胞移植後の再発リスク因子解析 | 矢野真吾 | ASH2011 ,他 | |
| 2-8 | AML移植後再発に対するDLIの有用性と予後予測因子の解析 | 高見昭良 | JSH2012 | |
| 2-12 | AML-M6/M7に対する造血幹細胞移植 | 石山謙 | JSHCT2012, 他 | |
| 2-23 | 成人AMLに対するiv Busulfanを用いた骨髄破壊的移植前治療による同種造血幹細胞移植の治療成績 | 山下卓也 | JSHCT2013, 他 | |
| 2-24 | 成人AMLに対するiv Busulfanを用いた骨髄非破壊的移植前治療による同種造血幹細胞移植の治療成績 | 山下卓也 | JSHCT2013, 他 | |
| 3-2 | 小児急性リンパ性白血病に対する骨髄破壊的移植と骨髄非破壊的移植の比較検討 | 加藤剛二 | JSHCT2012 | |
| 3-4 | 同種移植後再発小児ALLにおける同種再移植後の予後に関する検討 | 加藤元博 | JSHCT2012 | BMT 2012;47:1307 |
| 3-5 | 非寛解期小児ALLにおける移植成績 | 岡本康裕 | JSHCT2012 | |
| 3-6 | 小児・思春期ALL第二寛解期に対するアロ造血幹細胞移植前処置の影響 | 石田宏之 | JSHCT2012 | |

| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 3-12 | 小児急性白血病の移植前処置における経口ブスルファンと静注ブスルファンの比較 | 加藤元博 | JSH2013,他 | BBMT 2013;19:1690 |
| 4-1 | 高齢者 ALL 患者に対する RIST の有用性と予後因子に関する研究 | 金森平和 | ASH2011 | BMT 2013;48:1513 |
| 4-2 | Impact of donor sources on allogeneic stem cell transplantation for Philadelphia chromosome-negative acute lymphoblastic leukemia in first complete-remission. | 西脇聡史 | ASCO2012, 他 | Ann Oncol 2013;24:1594 |
| 4-3 | 急性リンパ球性白血病に対する軽減前処置造血細胞移植に関する後方視的解析および骨髄破壊的前処置移植との比較 | 田中淳司 | ASH2012 | BMT 2013;48:1389 |
| 4-4 | 成人フィラデルフィア染色体陰性急性リンパ性白血病における第一寛解期自家移植と同種移植の治療成績の比較 | 加藤春美 | ASH2012 | |
| 4-5 | Ph+ALL を対象とした造血幹細胞移植における予後因子解析 | 水田秀一 | | Blood in press |
| 5-2 | 慢性骨髄性白血病に対する同種造血幹細胞移植の成績 （CML 成人共同研究） | 村松秀城 | JSHCT2012 | |
| 6-1 | 慢性骨髄性白血病（CML）の同種移植の幹細胞別の移植成績の比較 | 大橋一輝 | JSH2012,他 | |
| 7-1 | 治療関連による小児および若年者の骨髄異形成症候群（MDS）/急性骨髄性白血病（AML）症例に対する造血幹細胞移植治療の検討 | 小嶋靖子 | JSHCT2012 | |
| 7-4 | 小児骨髄異形成症候群に対する同種造血幹細胞移植において G-CSF の予後に与える影響 | 長谷川大一郎 | JSH2011 | |
| 7-5 | 小児一次性骨髄異形成症候群に対する至適移植法の開発に関する研究 | 長谷川大一郎 | EBMT2013 | |
| 8-1 | 同種造血幹細胞移植が行われた 50 歳以上の MDS 患者における移植成績の検討 | 青木一成 | ASH2012 | |
| 8-3 | 成人 MDS に対する臍帯血移植 | 石山謙 | EHA2013,他 | |
| 8-4 | 慢性骨髄単球性白血病に対する同種造血幹細胞移植の有効性の検討 | 糸永英弘 | ASH2013 | |
| 9-2 | 小児における稀なリンパ腫の造血幹細胞移植症例の検討 | 小林良二 | International Symposium on Childhood, Adolescent and Young Adult Non –Hodgkin's Lymphoma 2012 | BJH 2012;159:88 |
| 9-4 | 小児未分化大細胞型リンパ腫に対する造血細胞移植成績 | 深野玲司 | JSH2013 | |

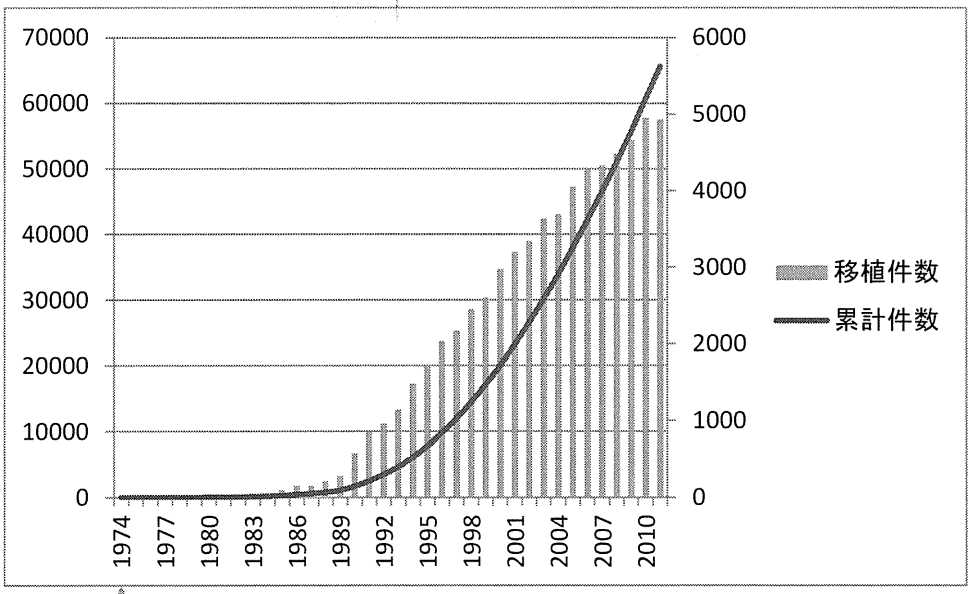
| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 9-6 | 小児成熟 B 細胞性腫瘍に対する造血細胞移植成績 | 藤田直人 | International Symposium on Childhood, Adolescent and Young Adult Non –Hodgkin's Lymphoma 2012 | |
| 10-1 | 濾胞性リンパ腫の造血幹細胞移植の後方視的研究 | 伊豆津宏二 | ASH2011,他 | |
| 10-2 | 悪性リンパ腫自家移植後再発に対する同種移植の有効性の検討 ― 一元化データを用いた解析 ― | 吾郷浩厚 | JSHCT2012 | |
| 10-3 | 節外性 NK/T 細胞リンパ腫、鼻型（ENKL）の移植成績 | 鈴木律朗 | ICML2011, 他 | |
| 10-4 | リンパ腫の組織型別・病期別移植成績 | 伊豆津宏二 | ICML2011, 他 | |
| 10-5 | ホジキンリンパ腫に対する造血幹細胞移植の後方視的検討 | 賀古真一 | JSHCT2012 | |
| 10-6 | 移植前 B 型肝炎、C 型肝炎ウイルスの感染状態が悪性リンパ腫の移植成績および有害事象に及ぼす影響 | 加藤春美 | JSH2013,他 | |
| 10-7 | 高齢者びまん性大細胞型 B 細胞リンパ腫の造血幹細胞移植の後方視的研究 | 千原大 | ICML2013 | BBMT (in press) |
| 10-8 | 縦隔(胸腺)大細胞型 B 細胞性リンパ腫に対する造血幹細胞移植の後方視的研究 | 近藤英生 | ICML2013 | |
| 10-9 | 中枢神経原発リンパ腫に対する造血幹細胞移植の後方視的研究 | 近藤英生 | EHA2013 | |
| 11-1 | フルダラビン導入が非血縁骨髄移植の成績に与える影響 | 矢部普正 | JSHCT2012 | |
| 11-2 | 小児再生不良性貧血における HLA 一致血縁者間骨髄移植と免疫抑制療法の比較 | 吉田奈央 | JSH2011,他 | |
| 11-3 | 小児再生不良性貧血におけるドナー選択 —HLA 一致血縁ドナー、不一致血縁ドナー、非血縁ドナーの比較 | 小島勢二 | JSH2011,他 | |
| 11-4 | 小児の HLA 一致同胞間移植における治療成績 | 菊地陽 | JSHCT2012 | BMT 2013;48:657 |
| 11-7 | 小児再生不良性貧血における骨髄移植後ドナータイプ造血不全の解析 | 吉田奈央 | ASH2012,他 | |
| 13-1 | ATL 患者に対する同種骨髄破壊的移植と非破壊的移植の比較検討 | 石田高司 | JSH2011 | Blood:2012;120:1734 |
| 13-2 | 成人 T 細胞性白血病／リンパ腫に対する臍帯血移植の後方視的検討 | 加藤光次 | JSH2012,他 | |
| 13-3 | ATL 患者に対する同種骨髄破壊的移植と非破壊的移植の比較検討、GVHD の意義について | 石田高司 | | BBMT 2013;19:1731 |

| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 14-2 | 造血幹細胞移植を施行した多発性骨髄腫での予後因子解析 | 高松博幸 | EHA2013,他 | |
| 15-2 | 造血幹細胞移植を併用する大量化学療法を施行したユーイング肉腫ファミリー腫瘍の治療成績 | 小川淳 | JSPHO2011 | |
| 15-3 | 小児肝芽腫に対する大量化学療法の有用性の検討 | 山本将平 | JSPHO2011 | |
| 15-4 | 神経芽腫に対する同種臍帯血移植の検討 | 高橋義行 | EBMT2012,他 | |
| 15-6 | 網膜芽細胞腫に対する造血幹細胞移植の検討 | 小林良二 | JSPHO2011 | |
| 15-7 | 横紋筋肉腫の造血幹細胞移植症例の検討 | 小林良二 | JSPHO2011 | |
| 15-8 | ウイルムス腫瘍および類縁疾患に対する造血幹細胞移植の検討 | 小林良二 | JSPHO2011 | |
| 16-3 | Diamond-Blackfan 貧血に対する同種造血細胞移植の成績 | 矢部普正 | JSHCT2012,他 | |
| 16-4 | Fanconi 貧血に対する同種造血細胞移植の成績 | 矢部みはる | JSHCT2012,他 | |
| 16-9 | 副腎白質ジストロフィーに対する同種造血細胞移植 | 加藤剛二 | JSHCT2013,他 | |
| 17-3 | 非血縁者間骨髄移植における年代別のアリル不適合の影響 | 神田善伸 | JSH2012 | BJH 2013;161:566 |
| 17-6 | Reduced intensity conditioning を用いた非血縁者間骨髄移植における HLA 不一致の影響 | 横山寿行 | JSHCT2013 | |
| 17-8 | KIR リガンド不適合が移植成績に及ぼす影響の検討 | 田中淳司 | EHA2013 | Blood Cancer J (in press) |
| 17-11 | T 細胞除去を用いない HLA 不一致親子間移植においてレシピエントとドナーとの血縁関係が移植成績に与える影響の検討 | 一戸辰夫 | ASH2012,他 | |
| 17-12 | 非血縁者間臍帯血移植における HLA 不適合度と移植成績 | 熱田由子 | EBMT2012,他 | Haematologica 2013;98:814 |
| 17-13 | 非血縁者間臍帯血移植における GVH 方向 HLA 不適合あるいは HVG 方向 HLA 不適合が移植成績に及ぼす影響 | 諫田淳也 | JSH2012 | BBMT 2013;19:247 |
| 17-14 | 非血縁者間骨髄移植における年代別の高リスクアリル不適合の影響 | 神田善伸 | | BBMT (in press) |
| 17-15 | 第一寛解期急性白血病に対する同種移植における、ドナー選択に関する臨床決断分析 –GVH 方向 HLA 一抗原不適合血縁者と HLA8/8 アリル適合非血縁者の比較 | 諫田淳也 | JSHCT2013,他 | |
| 18-2 | 年齢、体重、性別、疾患別にみたドナー別・ソース別の造血細胞移植実施状況と成績比較 | 加藤俊一 | JSPHO2012 | |
| 18-4 | 非血縁者間移植の至適ドナーの検討を目的とした国際共同研究 | 鍬塚八千代 | EBMT2013,他 | BBMT (in press) |

| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 18-6 | 急性白血病、慢性白血病急性転化および骨髄異形成症候群に対する同種造血幹細胞移植における移植ソースの影響および化学療法との比較 | 田中正嗣 | JSH2013 | |
| 18-8 | 非血縁者間臍帯血移植とGVH方向1抗原以内不適合血縁者間移植の移植成績の比較 | 諫田淳也 | JSH2012 | Leukemia 2013;27:286 |
| 18-9 | ABO血液型不適合が同種移植成績に与える影響—移植細胞ソースによる違い | 木村文彦 | JSH2012 | |
| 18-10 | 重症再生不良性貧血に対する血縁者間造血細胞移植成績の国際比較 | 木村文彦 | EHA2013 | |
| 18-12 | HLA一致血縁ドナーからの成人造血悪性腫瘍に対する骨髄破壊的前処置による同種造血幹細胞移植　移植ソース　骨髄と末梢血幹細胞の比較 | 長藤宏司 | JSH2012 | |
| 19-1 | シクロスポリンおよびタクロリムスによるＧＶＨＤ予防法の比較検討 | 酒井リカ | EBMT2012,他 | |
| 19-2 | 血液悪性腫瘍に対する同種造血細胞移植における抗リンパ球グロブリンの臨床的検討 | 加藤剛二 | JSH2012,他 | |
| 19-5 | 既存データを用いた年齢別の急性GVHD発症後の予後の検討 | 中根孝彦 | JSH2012,他 | |
| 19-6 | 急性GVHDに対するステロイド一次治療の成績 | 村田誠 | JSHCT2012,他 | BBMT 2013;19:1183 |
| 19-7 | GVHDとTMAの関連性の検討 | 吾郷浩厚 | JSH2012 | |
| 19-8 | 既存データを用いた臓器別慢性GVHDの発症様式、発症頻度、予後の解析 | 諫田淳也 | JSH2012 | BMT (in press) |
| 19-9 | 一元化管理事業データに基づく造血幹細胞移植後の閉塞性細気管支炎の解析 | 仲宗根秀樹 | JSHCT2012 | Transpl Int 2013;26:631 |
| 19-10 | GVHDとGVL効果に対するドナーとレシピエントの性別の影響 | 大島久美 | Tandem2012,他 | |
| 20-1 | 造血幹細胞移植後サイトメガロウイルス感染症の発症頻度、危険因子、予防法に関する研究 | 西田徹也 | JSHCT2013 | |
| 20-2 | 非血縁者間移植患者におけるウイルス感染症の検討 | 森有紀 | JSH2013 | |
| 20-3 | 同種造血幹細胞移植後の出血性膀胱炎（HC）に対する標準的予防法・早期治療法の確立に向けた抗ウイルス薬のHC発症抑制効果に関する検討 | 中沢洋三 | JSHCT2013 | |
| 20-4 | 造血幹細胞移植後合併症と長期予後に与えるHCV既感染の影響 | 仲宗根秀樹 | JSHCT2012,他 | Am J Hematol 2013;88:477 |
| 20-5 | 同種造血幹細胞後の深在性真菌症に関する検討 | 大島久美 | JSH2012,他 | |
| 20-6 | 一元管理事業データに基づく同種造血幹細胞移植後の器質化肺炎(COP/BOOP)の解析 | 仲宗根秀樹 | JSH2012 | BMT :2013;48:1317 |

| 研究番号 | 課題名 | PI | 学会発表 | 論文 |
|---|---|---|---|---|
| 20-7 | Hematopoietic Cell Transplantation Specific Comorbidity Index (HCT-CI)を用いた同種造血幹細胞移植後の予後予測に関する研究 | 横山洋紀 | JSHCT2012 | |
| 20-8 | 同種造血幹細胞移植後の類洞閉塞症候群の発症割合、リスク因子ならびに治療法に関する研究 | 藥師神公和 | ASH2013 | |
| 20-9 | 同種造血幹細胞移植後の微小血管症の発症割合、リスク因子、予後に関する研究 | 名和由一郎 | JSHCT2012 | |
| 20-10 | 小児および成人における移植後非感染性肺合併症に関する検討 | 鬼塚真仁 | JSHCT2013 | |
| 20-11 | 造血幹細胞移植後ウイルス感染の造血器悪性腫瘍再発に及ぼす影響に関する研究 | 竹中克斗 | JSHCT2013 | |
| 20-12 | 小児に対する同種造血幹細胞移植後の生着不全に対する再移植の予後 | 加藤元博 | JSH2012,他 | BMT 2013;48:1173 |
| 20-13 | 同種造血幹細胞移植前の糖尿病が予後に与える影響について | 高野久仁子 | JSHCT2013 | |
| 20-16 | 血小板生着不全のリスク因子と予後に及ぼす影響 | 木村文彦 | JSHCT2013,他 | |
| 20-19 | 同種造血幹細胞移植前のBMIと予後の関連について | 藤重夫 | JSH2013 | |
| 21-4 | 同種造血幹細胞移植における晩期死亡と死因の解析 | 熱田由子 | JSH2012,他 | |
| 21-7 | 同種造血幹細胞移植後の晩期再発に関する検討 | 山下卓也 | ASH2013 | |
| 22-1 | Safety and risk of allogeneic peripheral blood stem cell donation: results of nation-wide consecutively prereistered 3,264 family donor survey in comparison with bone marrow donation in Japan | 小寺良尚 | ASH2010 | BMT 2014;49:195 |
| 22-2 | 同種造血細胞ドネイションの更なる促進のために | 小寺良尚 | JSHCT2011 | |
| 22-3 | 血縁造血幹細胞ドナーの声 | 小寺良尚 | | 日本造血細胞移植学会雑誌 2012;1:6 |
| 22-5 | 小児骨髄移植ドナーの安全性 | 矢部みはる | JSHCT2013 | |
| 23-1 | 海外非血縁ドナーからの造血幹細胞移植の成績に関する検討　～国内非血縁ドナーからの骨髄移植・さい帯血移植とのmatched-pair解析 | 一戸辰夫 | APBMT2012,他 | |

## 5. 移植登録数と公表論文数の推移




第一例目の移植

日本小児血液学会登録開始

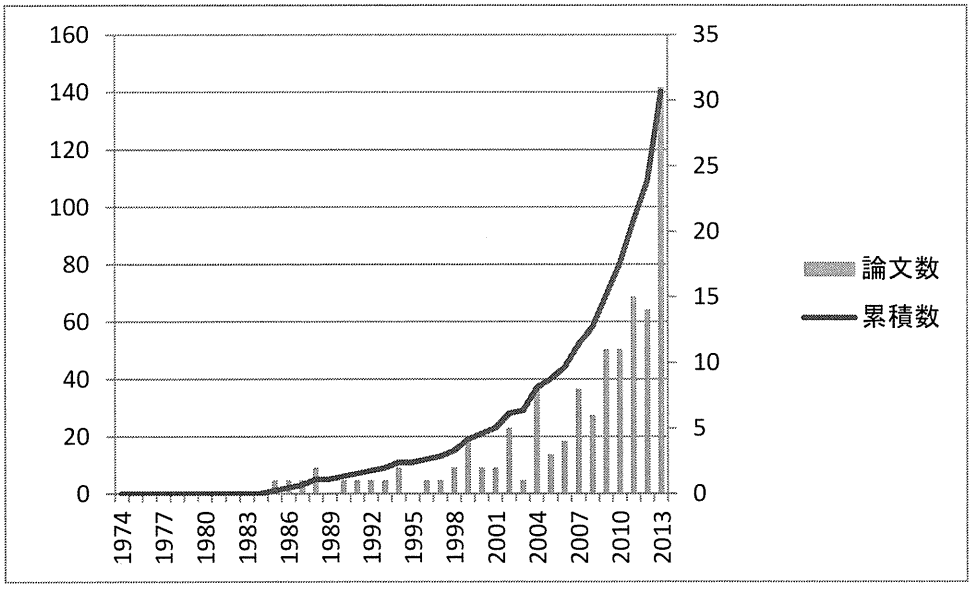
日本造血細胞移植学会登録開始

骨髄移植推進財団設立

日本さい帯血バンクネットワーク設立

TRUMP運用開始

ワーキンググループ発足



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（免疫アレルギー疾患等予防・治療研究事業　移植医療研究分野）

# 本邦における造血細胞移植一元化登録研究システムの確立

平成 23～25 年度　総合研究報告書

2／2冊

研究代表者　熱田　由子

平成 26（2014）年 3 月

# 目　　次

### Definitions

Hematopoietic recovery was defined as time to ANC $\geqslant 0.5 \times 10^9$/L, time to reticulocytes $\geqslant 10‰$ and time to platelets $\geqslant 50 \times 10^9$/L for 3 consecutive days. Engraftment failure was defined as no neutrophil recovery by day 60. Acute and chronic GVHD were diagnosed and graded according to established criteria.[15,16] Based on the report by the Center for International Blood and Marrow Transplant Research (CIBMTR),[17] the conditioning regimens were classified as myeloablative if TBI >8 Gy, oral BU $\geqslant$9 mg/kg, i.v. BU $\geqslant$7.2 mg/kg or melphalan >140 mg/m$^2$ was included in the conditioning regimen, whereas other conditioning regimens were classified as nonmyeloablative.

### End points

The primary end point was OS. The secondary end points were engraftment, GVHD, relapse and NRM.

### Statistical analysis

The probabilities of hematopoietic recovery, acute and chronic GVHD, relapse and NRM were estimated on the basis of cumulative incidence curves.[18] The probability of OS was estimated according to the Kaplan–Meier method.[19] The groups were compared using the log-rank test. Competing risk regression analysis was used to identify factors associated with NRM. The adjusted probability of OS was estimated using Cox's proportional hazards model, with consideration of other significant clinical variables in the final multivariate models.[20] All variables significant at $P<0.10$ on univariate analysis were included in multivariate stepwise analyses. All tests were two sided, and $P<0.05$ was considered significant. The data were analyzed by STATA version 12 statistical software (StataCorp, College Station, TX, USA).

## RESULTS

### Patient and transplantation characteristics

A total of 83 patients met the inclusion criteria. Patient and transplantation characteristics are summarized in Table 1. The median age at transplantation was 53 years, and most patients (66%) were male. Transplants were performed between 1993 and 2009, but the majority (90%) of them were performed after 2000. This population consisted of 47 BM transplants, 25 PBSC transplants and 11 UCB transplants. Of the 44 related donor transplants, 40 (91%) were performed from serological HLA-A, B and DR 6/6 matched donor; 28 unrelated BM transplants included 16 (57%) HLA-A, B and DRB1 alleles 6/6 matched donors and 11 (39%) HLA-A, B and DRB1 alleles 5/6 matched donors; all (100%) unrelated UCB transplants were performed from serological HLA-A, B and DR 5/6 or 4/6 matched donors. Most patients (76%) received a nonmyeloablative regimen. The median follow-up for living patients was 40 (range, 0.4–150) months.

### Engraftment

Seven patients (8%) died without engraftment within 60 days after transplantation, including heart failure on day 5 after UCB transplant ($n=1$), primary disease on day 7 after related PBSC transplant ($n=1$), infection on day 11 after unrelated BM transplant ($n=1$), multiple organ failure on day 12 after unrelated BM transplant ($n=1$), heart failure on day 18 after unrelated BM transplant ($n=1$), infection on day 30 after unrelated BM transplant ($n=1$) and thrombotic microangiopathy on day 56 after UCB transplant ($n=1$). Another patient (1%) received a second transplant on day 28 because of lack of engraftment signs at that time.

Neutrophil recovery on day 60 occurred in 92% (95% confidence interval (CI), 57–99%) of related BM, 92% (71–98%) of related PBSCs, 79% (58–90%) of unrelated BM and 82% (45–95%) of unrelated UCB (Figure 1a). Unrelated BM and unrelated UCB (vs related BM) transplantations were significantly associated with a lower probability of neutrophil recovery ($P=0.015$ and $P=0.016$, respectively), whereas related PBSC transplantation was

**Table 1.** Patient and transplantation characteristics ($n=83$)

| | N (%) |
|---|---|
| *Age at transplant, evaluable* n | 83 |
| 21–39 Years | 9 (11) |
| 40–49 Years | 22 (27) |
| 50–59 Years | 37 (44) |
| 60–79 Years | 15 (18) |
| Median age (range), years | 53 (21–79) |
| *Sex, evaluable* n | 83 |
| Female | 28 (34) |
| Male | 55 (66) |
| *Transplant year, evaluable* n | 83 |
| 1993–1999 | 8 (10) |
| 2000–2004 | 22 (27) |
| 2005–2009 | 53 (63) |
| *Performance status at transplant, evaluable* n | 70 |
| 0–1 | 54 (77) |
| $\geqslant$2 | 16 (23) |
| *Time from diagnosis to transplant, evaluable* n | 80 |
| <1 Years | 33 (41) |
| 1–2 Years | 16 (20) |
| $\geqslant$2 Years | 31 (39) |
| Median (range), years | 1.5 (0.1–21.0) |
| *Frequency of RBC transfusion before transplant, evaluable* n | 51 |
| $\leqslant$9 | 26 (51) |
| 10–19 | 8 (16) |
| $\geqslant$20 | 17 (33) |
| *Frequency of PLT transfusion before transplant, evaluable* n | 51 |
| $\leqslant$9 | 38 (74) |
| 10–19 | 4 (8) |
| $\geqslant$20 | 9 (18) |
| *Use of JAK2 inhibitor before transplant, evaluable* n | 77 |
| Yes | 0 (0) |
| No | 77 (100) |
| *Splenectomy before transplant, evaluable* n | 78 |
| Yes | 2 (3) |
| No | 76 (97) |
| *DIPSS at transplant* | 78 |
| Low | 8 (10) |
| Intermediate-1 | 17 (22) |
| Intermediate-2 | 50 (64) |
| High | 3 (4) |
| *Splenomegaly at transplant* | 78 |
| Yes | 59 (76) |
| No | 19 (24) |
| *CMV serostatus, evaluable* n | 58 |
| Negative | 5 (9) |
| Positive | 53 (91) |
| *Donor source, evaluable* n | 83 |
| Related BM | 19 (23) |
| Related PBSCs | 25 (30) |
| Unrelated BM | 28 (34) |
| Unrelated umbilical cord blood | 11 (13) |
| *Sex matching between patient and donor, evaluable* n | 71 |
| Match | 35 (49) |
| Female patient and male donor | 15 (21) |
| Male patient and female donor | 21 (30) |
| *ABO matching between patient and donor, evaluable* n | 65 |
| Match | 34 (52) |
| Mismatch | 31 (48) |
| *Preconditioning regimen, evaluable* n | 71 |
| Myeloablative | 17 (24) |
| Nonmyeloablative | 54 (76) |
| *Prophylaxis for GVHD, evaluable* n | 81 |
| CsA based | 37 (46) |
| Tacrolimus based | 42 (52) |
| Others | 2 (2) |
| *Use of JAK2 inhibitor after transplant, evaluable* n | 78 |
| Yes | 0 (0) |
| No | 78 (100) |

Abbreviations: DIPSS = Dynamic International Prognostic Scoring System; JAK2 = Janus kinase 2.

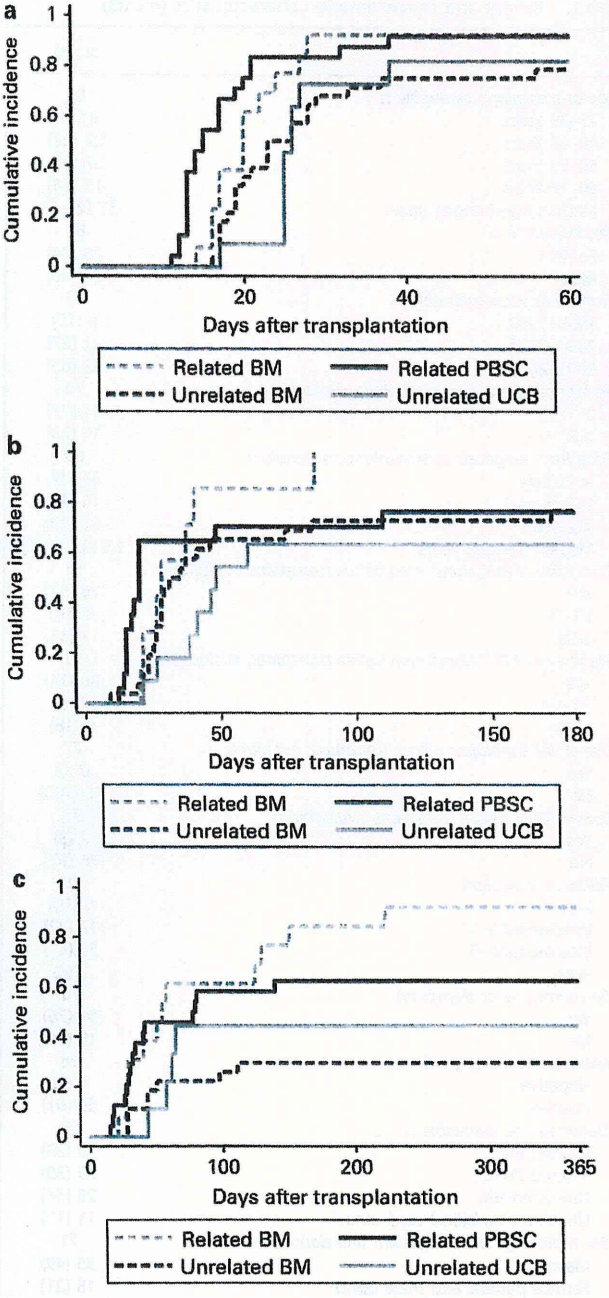


**Figure 1.** Hematopoietic recoveries after transplantation in PMF patients. **(a)** Cumulative incidences of neutrophil recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown. **(b)** Cumulative incidences of reticulocyte recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown. **(c)** Cumulative incidences of platelet recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown.

not significantly different from related BM transplantation ($P=0.46$). The median days for neutrophil recovery in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 20, 14, 21 and 25, respectively.

Reticulocyte recovery on day 180 occurred in 100% of related BM, 75% (46–90%) of related PBSC, 77% (56–89%) of unrelated BM and 64% (30–85%) of unrelated UCB transplantations (Figure 1b). Unrelated UCB (vs related BM) transplantation was significantly associated with a lower probability of reticulocyte recovery ($P=0.012$), whereas related PBSC and unrelated BM transplantations were not significantly different from related BM transplantation ($P=0.57$ and $P=0.076$, respectively). The median days for reticulocyte recovery in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 28, 17, 28 and 41, respectively.

Platelet recovery on day 365 occurred in 92% (57–99%) of related BM, 63% (40–78%) of related PBSC, 30% (14–47%) of unrelated BM and 44% (14–72%) of unrelated UCB transplantations (Figure 1c). Unrelated BM and unrelated UCB transplantations (vs related BM) were significantly associated with a lower probability of platelet recovery ($P<0.001$ and $P=0.027$, respectively), whereas related PBSC transplantation was not significantly different from related BM transplantation ($P=0.20$). The median days for platelet engraftment in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 50, 32, 43 and 57, respectively.

## GVHD

The incidences of grade II–IV and III–IV acute GVHD on day 100 were 17% (95% CI, 4–37%) and 6% (0–22%) in related BM, 32% (15–50%) and 16% (5–33%) in related PBSC, 29% (14–46%) and 14% (4–30%) in unrelated BM and 10% (1–36%) and 0% in unrelated UCB transplantations, respectively. There was no significant difference in the incidence of grade II–IV acute GVHD among stem cell sources, whereas the incidence of grade III–IV acute GVHD was significantly lower after unrelated UCB transplantation than after related BM transplantation ($P<0.001$).

The incidences of chronic GVHD at 2 years after transplantation were 35% (95% CI, 14–57%) in related BM, 52% (31–69%) in related PBSC, 25% (11–42%) in unrelated BM and 18% (3–44%) in unrelated UCB transplantations. There was no significant difference in the incidence of chronic GVHD among stem cell sources.

## Relapse

Relapse rates at 2 and 5 years after transplantation were 5% (95% CI, 0–21%) and 12% (2–33%) in related BM, 8% (1–22%) and 12% (3–28%) in related PBSC and 4% (0–18%) and 4% (0–18%) in unrelated BM transplantations, respectively. No patient relapsed after UCB transplantation, in which the longest follow-up was 48 months.

## NRM

NRM rates at 2 and 5 years after transplantation were 33% (95% CI, 13–54%) and 33% (13–54%) in related BM, 45% (24–63%) and 50% (28–69%) in related PBSC and 61% (38–77%) and 61% (38–77%) in unrelated BM transplantations, respectively (Figure 2). NRM at 2 years after unrelated UCB transplantation was 64% (30–85%), and NRM at 5 years after UCB transplantation was not evaluable because of lack of patients alive beyond 5 years after transplantation. NRM rates after related PBSC and unrelated BM transplantation were not significantly different from that after related BM transplantation ($P=0.28$ and $P=0.068$, respectively), whereas unrelated UCB transplantation (vs related BM) was significantly associated with a significantly higher NRM ($P=0.021$).

To identify predictive factors for higher NRM, multivariate analysis for all clinical features listed in Table 1 was performed, and the final multivariate model is shown in Table 2. PS $\geqslant 2$ and unrelated BM were predictive factors for higher NRM. For patients with performance status (PS) 0–1 ($n=54$), NRM rates at 2 and 5 years after transplantation were 37% (23–50%) and 40% (26–54%),

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# Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease

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**Background:** The number of long-term survivors after hematopoietic stem cell transplantation (HSCT) showed steady increase in the past two decades. Second malignancies after HSCT are a devastating late complication. We analyzed the incidence of, risk compared with that in the general population, and risk factors for secondary solid cancers.

**Patients and methods:** Patients were 17 545 adult recipients of a first allogeneic stem cell transplantation between 1990 and 2007 in Japan. Risks of developing secondary solid tumors were compared with general population by using standard incidence ratios (SIRs).

**Results:** Two-hundred sixty-nine secondary solid cancers were identified. The cumulative incidence was 0.7% [95% confidence interval (CI), 0.6%–0.9%] at 5 years and 1.7% (95% CI, 1.4%–1.9%) at 10 years after transplant. The risk was significantly higher than that in the general population (SIR = 1.8, 95% CI, 1.5–2.0). Risk was higher for oral cancer (SIR = 15.7, 95% CI, 12.1–20.1), esophageal cancer (SIR = 8.5, 95% CI, 6.1–11.5), colon cancer (SIR = 1.9, 95% CI, 1.2–2.7), skin cancer (SIR = 7.2, 95% CI, 3.9–12.4), and brain/nervous system cancer (SIR = 4.1, 95% CI, 1.6–8.4). The risk of developing oral, esophageal, or skin cancer was higher at all times after 1-year post-transplant. Extensive-type chronic graft-versus-host disease (GVHD) was a significant risk factor for the development of all solid tumors (RR = 1.8, $P < 0.001$), as well as for oral (RR = 2.9, $P < 0.001$) and esophageal (RR = 5.3, $P < 0.001$) cancers. Limited-type chronic GVHD was an independent risk factor for skin cancers (RR = 5.8, $P = 0.016$).

**Conclusion:** Recipients of allogeneic HSCT had a significantly higher ~2-fold risk of developing secondary solid cancers than the general population. Lifelong screening for high-risk organ sites, especially oral or esophageal cancers, is important for recipients with active, or a history of, chronic GVHD.

**Key words:** secondary solid cancers, late effect, hematopoietic stem cell transplantation

## introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment of choice for malignant and non-malignant hematological disorders [1]. The annual number of allogeneic HSCT has increased steadily over the past three decades worldwide [2–6]. Progress in transplant procedures in addition to this steady increase in the number of HSCT procedures worldwide has contributed to an increase in the number of long-term survivors.

Secondary malignancies, including new solid cancers, are an important cause of late mortality. Several studies have reported that survivors of HSCT have a 2–3-fold increased risk of

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developing new solid cancers compared with an age-, sex-, region-, and calendar-year-adjusted population and the risk among long-term survivors ranges from 1% to 6% at 10 years after transplantation [7–14]. Identified risk factors include exposure to radiation as a part of the conditioning regimen and chronic graft-versus-host disease (GVHD), and the latter has been shown to be strongly correlated with the development of squamous cell carcinoma [8, 10, 12, 15–17]. However, a recent long-term follow-up analysis of patients who were transplanted after myeloablative doses of busulfan and cyclophosphamide without total body irradiation (TBI) found a similar increased incidence of 0.6% at 5 years and 1.2% at 10 years after transplantation [13]. We conducted a nationwide, retrospective cohort study with a large and different cohort from those used in previous reports from North America and Europe, to determine the incidence and risks of developing secondary solid cancers.

## methods

### data source and collection of data

The recipient clinical data were collected by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) using the Transplant Registry Unified Management Program, as described previously [18]. The JSHCT collect recipients' baseline, disease, transplant, and transplant outcome information who received HSCT in the previous year. Patient information regarding survival, disease status, and long-term complications including chronic GVHD and second malignancies are renewed annually. This study was approved by the data management committee of the JSHCT, as well as the institutional review board of Nagoya University Graduate School of Medicine.

### patients

Adult patients (at least 16 years of age) who received a first HSCT between 1990 and 2007 were considered as subjects for the present study. Those who were inherently susceptible to developing cancer [Fanconi anemia ($N = 3$) and congenital immunodeficiency ($N = 12$)] were excluded. Three-hundred five recipients (1.7%) were excluded because of insufficient follow-up data. The study included 17 545 recipients; 5358 recipients of related bone marrow, 3587 recipients of related peripheral blood stem cells (including 134 bone marrow and peripheral blood stem cells combined), 6508 recipients of unrelated bone marrow, and 2092 recipients of unrelated cord blood.

### statistical analysis

Standard incidence ratios (SIRs) were calculated to determine whether the number of recipients in the present cohort who developed secondary solid tumor after receiving a HSCT was different than that in the general population (supplementary method, available at *Annals of Oncology* online). Cumulative incidences of solid cancer or GVHD were estimated by taking into account the competing risk of death among patients who did not develop a second malignancy or GVHD [19]. The influence of potential risk factors was estimated by using the Cox proportional hazard model [20]. A stepwise multivariate approach was used to identify the most important predictor with respect to the development of secondary solid cancers. The variables considered were age at transplant, patient sex, donor-type (related versus unrelated), graft source, TBI as part of the conditioning regimen, reduced-intensity conditioning, grade 2–4 acute GVHD, and chronic GVHD. The model was stratified into four categories according to the primary disease; acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and others. Acute and chronic GVHD were considered as time-dependent covariates. TBI and chronic GVHD were frequent risk factors and were always kept in the model. Risk factors for high-risk cancer sites with adequate numbers of events for analyses were also analyzed: oral cavity/pharynx, esophagus, colon, and skin. The models for high-risk cancer sites were stratified according to the primary disease as described, and patient age at transplantation (<19, 20–29, 30–39, 40–49, 50–59, and >60), and also adjusted by patient age as a continuous variable. All *P*-values were two-sided.

## results

### patient and transplant characteristics

Table 1 shows the patient characteristics, their disease, and transplant regimens for 17 545 recipients of a first HSCT. The cumulative incidences of grade 2–4 acute GVHD at 150 days and chronic GVHD at 2 years post-transplant were 35% [95% confidence interval (CI), 35%–36%] and 41% (95% CI, 40%–41%), respectively. The observation period reached 69 465 person-years among the subjects for analyses. Of the 17 545 recipients, 5864 had survived for 5 or more years, and 2192 recipients had survived 10 or more years at the time of analysis (Table 2).

### incidence and types of secondary solid cancers

The cumulative incidence of solid cancers was 0.7% (95% CI, 0.6–0.9) at 5 years, 1.7% (95% CI, 1.4–1.9) at 10 years, and 2.9% (95% CI, 2.5–3.4) at 15 years after transplantation (Figure 1). Two-hundred sixty-nine solid cancers were identified. Multiple solid cancers were observed in 11 patients. Nineteen recipients were diagnosed within 1-year post-transplantation (Table 2).

### risk compared with the general population

HSCT recipients had a 1.8-fold higher risk of invasive solid cancers compared with the general population (95% CI, 1.5–2.0). SIR was significantly higher for cancers of the oral cavity/pharynx (SIR = 15.7), esophagus (SIR = 8.5), colon (SIR = 1.9), skin (SIR = 7.2), and brain/nervous system (SIR = 4.1; Table 2). The risks of developing secondary cancers of the oral cavity/pharynx, esophagus, and skin were significantly higher than those in the general population throughout all periods after 1 year (Figure 2). The risk for developing colon cancer was elevated during the period of 1–4 years (SIR = 2.7), whereas the risks for developing cancer of the pancreas (SIR = 4.5) were elevated during the period of 5–9 years. Recipients were at higher risk of developing cancers of the rectum (SIR = 3.6) and the brain/nervous system (SIR = 19.1) after 10 years post-transplantation. The risk of developing secondary solid cancers of all types compared with the general population increased with the time since transplantation. This trend was observed for oral/pharynx and esophageal cancer (Table 2; Figure 2).

### recipients' age at transplantation and risks for developing secondary solid cancers

SIRs were also analyzed according to the recipient's age at transplantation (Table 3). Compared with the general population in Japan, the SIRs were significantly increased for all solid cancers, oral/pharynx, esophagus, liver, bronchus/lung, and brain/nervous system for recipients who were 16–19 years of age at transplant, all solid cancers, oral/pharynx, and esophagus for recipients who

Table 1. Patient, disease, and transplant characteristics

| Characteristics | Number | Percent |
|---|---|---|
| Total number | 17 545 | |
| Year of transplant | | |
| 1990–1994 | 1630 | 9 |
| 1995–1999 | 3750 | 21 |
| 2000–2004 | 7078 | 40 |
| 2005–2007 | 5087 | 29 |
| Patient sex | | |
| Male | 10 386 | 59 |
| Female | 7149 | 41 |
| Missing | 10 | <1 |
| Patient age | | |
| Median (range) | 40 (16–85) | |
| 16–19 | 1399 | 8 |
| 20–29 | 3506 | 20 |
| 30–39 | 3787 | 22 |
| 40–49 | 4167 | 24 |
| 50–59 | 3549 | 20 |
| ≥60 | 1137 | 6 |
| Diagnosis | | |
| Acute myeloid leukemia | 6096 | 35 |
| Acute lymphoblastic leukemia | 3334 | 19 |
| Chronic myeloid leukemia | 2514 | 14 |
| Myelodysplastic syndromes | 1716 | 10 |
| Adult T-cell leukemia | 591 | 3 |
| Other leukemia | 130 | 1 |
| Myeloproliferative disorders | 224 | 1 |
| Non-Hodikin's lymphoma | 1652 | 9 |
| Hodikin's lymphoma | 46 | <1 |
| Other lymphoma/type missing | 54 | <1 |
| Multiple myeloma | 210 | 1 |
| Aplastic anemia | 745 | 4 |
| Pure red cell aplasia | 4 | <1 |
| Paroxysmal nocturnal hemoglobinuria | 20 | <1 |
| Solid tumor | 109 | 1 |
| Others | 86 | <1 |
| Data missing | 14 | <1 |
| Donor | | |
| Related, siblings | 7825 | 45 |
| Related, other relatives | 941 | 5 |
| Related, data missing | 179 | 1 |
| Unrelated | 8600 | 49 |
| Stem cell source | | |
| Bone marrow | 11 866 | 68 |
| Peripheral blood | 3453 | 20 |
| Bone marrow and peripheral blood | 134 | 1 |
| Cord blood | 2092 | 12 |
| Conditioning regimen | | |
| Myeloablative | | |
| Cyclophosphamide + TBI ± other | 8298 | 47 |
| Other TBI regimen | 1321 | 8 |
| Busulfan + cyclophosphamide ± other | 2798 | 16 |
| Other non-TBI regimen | 778 | 4 |
| Reduced intensity | | |
| Fludarabine + busulfan ± other | 1527 | 9 |
| Fludarabine + cyclophosphamide ± other | 503 | 3 |
| Fludarabine + melphalan ± other | 1480 | 8 |
| Other RIST | 631 | 4 |
| Data missing | 209 | 1 |
| GVHD prophylaxis | | |
| No | 85 | <1 |
| Cyclosporine A + sMTX | 10 091 | 58 |
| Cyclosporine A ± other | 1175 | 7 |
| Tacrolimus + sMTX | 4682 | 27 |
| Tacrolimus ± other | 876 | 5 |
| Other | 323 | 2 |
| Data missing | 312 | 2 |

TBI, total body irradiation; sMTX, short-term methotrexate.

were 20–29 years of age at transplant, all solid cancers, oral/pharynx, esophagus, and gallbladder for recipients who were 30–39 years of age at transplant, all solid cancers, oral/pharynx, esophagus, and skin for recipients who were 40–49 years of age at transplant, all solid cancers, oral/pharynx, esophagus, colon, and skin for recipients who were 50–59 years of age at transplant (Table 3).

### risk factors for the development of secondary solid cancers

Extensive-type chronic GVHD and age at transplantation were important risk factors for the development of secondary solid cancers (Table 4). The risk was not increased in recipients who received TBI for conditioning. The results were similar when subjects were limited to those who received myeloablative conditioning (RR = 1.5, $P = 0.069$ for limited-type chronic GVHD, RR = 1.9, $P < 0.001$ for extensive-type chronic GVHD, and RR = 0.9, $P = 0.751$ for TBI). Risk factor analyses for high-risk organs with more than 10 cancer cases revealed that extensive-type chronic GVHD was an independent risk factor for cancers in the oral cavity/pharynx and esophagus. Limited-type chronic GVHD was a risk factor for cancers of skin (Table 4). For secondary cancers which developed within 1-year post-transplant, the only risk factor identified was older age at transplant (age 60 years or older; supplementary Table, available at *Annals of Oncology* online).

## discussion

Our main objective was to determine the incidence of, the risk compared with the general population, and risk factors for secondary solid tumors after allogeneic stem cell transplantation in a large cohort of adult recipients. Allogeneic HCT recipients were at higher risk of developing cancers of the oral cavity, esophagus, colon, and skin. The incidence and SIR of developing all solid cancers continued to increase with follow-up, which suggested a continuous increase as follow-up progressed. Our data are important since we included a large number of subjects and person-years of follow-up, in a transplant cohort that is different from those in previously reported large studies.

**Table 2.** Standard incidence ratio, ratio of observed versus expected number of secondary solid cancers according to duration post-transplant

| | Time since transplantation (years) | | | | | | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | | 1–4 | | 5–9 | | 10 or longer | | | | |
| Number of recipients | 17 545 | | 10 210 | | 5864 | | 2192 | | 17 545 | | |
| Person-years at risk | 12 803 | | 30 599 | | 18 845 | | 7218 | | 69 465 | | |
| Secondary cancer sites | O | SIR | O | SIR | O | SIR | O | SIR | O/E | SIR | 95% CI |
| All solid cancers | 19 | 0.7 | 97 | 1.5* | 90 | 2.0* | 63 | 3.1* | 269/153.6 | 1.8* | 1.5–2.0 |
| Oral/pharynx | 0 | 0.0 | 16 | 9.5* | 27 | 23.4* | 21 | 38.5* | 64/4.1 | 15.7* | 12.1–20.1 |
| Esophagus | 0 | 0.0 | 13 | 6.5* | 17 | 12.6* | 11 | 16.8* | 41/4.8 | 8.5* | 6.1–11.5 |
| Stomach | 2 | 0.4 | 7 | 0.6 | 6 | 0.8 | 1 | 0.3 | 16/26.0 | 0.6 | 0.4–1.0 |
| Colon | 2 | 0.8 | 16 | 2.7* | 5 | 1.2 | 4 | 2.2 | 27/14.3 | 1.9* | 1.2–2.7 |
| Rectum | 0 | 0.0 | 1 | 0.2 | 0 | 0.0 | 5 | 3.6* | 6/10.7 | 0.6 | 0.2–1.2 |
| Liver | 1 | 0.6 | 5 | 1.4 | 0 | 0.0 | 2 | 1.8 | 8/8.6 | 0.9 | 0.4–1.8 |
| Gallbladder | 2 | 5.1 | 2 | 2.1 | 2 | 3.0 | 0 | 0.0 | 6/2.3 | 2.6 | 1.0–5.7 |
| Pancreas | 0 | 0.0 | 2 | 1.0 | 6 | 4.5* | 1 | 1.6 | 9/4.7 | 1.9 | 0.9–3.7 |
| Broncus/lung | 3 | 1.2 | 4 | 0.6 | 9 | 2.1 | 3 | 1.5 | 19/15.1 | 1.3 | 0.8–2.0 |
| Skin | 2 | 7.0 | 6 | 8.1* | 3 | 5.7* | 2 | 8.4* | 13/1.8 | 7.2* | 3.9–12.4 |
| Female breast | 0 | 0.0 | 3 | 0.3 | 1 | 0.1 | 3 | 0.9 | 7/24.5 | 0.3 | 0.1–0.6 |
| Cervix uteri | 1 | 1.3 | 4 | 2.0 | 1 | 0.7 | 1 | 1.6 | 7/4.8 | 1.5 | 0.6–3.0 |
| Corpus uteri | 2 | 3.7 | 1 | 0.7 | 2 | 1.8 | 0 | 0.0 | 5/3.6 | 1.4 | 0.4–3.2 |
| Ovary | 0 | 0.0 | 1 | 0.7 | 1 | 1.0 | 1 | 2.2 | 3/3.6 | 0.8 | 0.2–2.4 |
| Prostate | 1 | 1.2 | 0 | 0.0 | 1 | 0.6 | 1 | 1.4 | 3/5.4 | 0.6 | 0.1–1.6 |
| Bladder | 1 | 1.9 | 3 | 2.4 | 0 | 0.0 | 0 | 0.0 | 4/2.9 | 1.4 | 0.4–3.5 |
| Kidney | 0 | 0.0 | 1 | 0.6 | 1 | 0.9 | 0 | 0.0 | 2/4.1 | 0.5 | 0.1–1.8 |
| Brain/nervous system | 1 | 3.4 | 1 | 1.4 | 1 | 2.1 | 4 | 19.1* | 7/1.7 | 4.1* | 1.6–8.5 |
| Thyroid | 0 | 0.0 | 2 | 1.1 | 2 | 1.5 | 0 | 0.0 | 4/4.5 | 0.9 | 0.2–2.3 |
| Other[a] | 1 | | 9 | | 4 | | 3 | | 17 | | |

[a]Other sites included two testicular cancers, four connective tissue cancers, four bone cancers, one larynx cancer, one malignant salivary gland tumor, one duodenum papilla cancer, one germ cell tumor, one carcinomatous pleurisy of origin unknown, and two squamous cell carcinomas of unknown origin.
*$P < 0.05$.

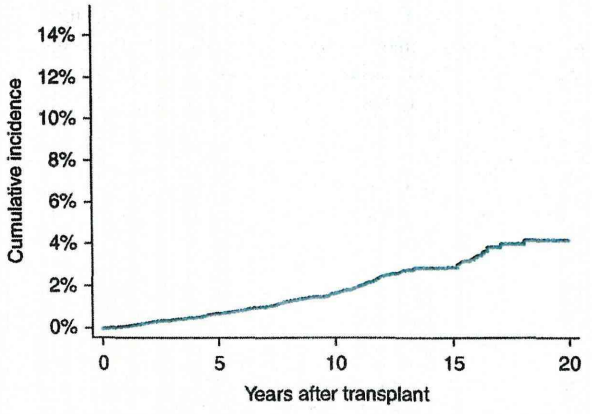


**Figure 1.** Cumulative incidence of developing a secondary solid cancer. The cumulative incidence of solid cancers was 0.7% [95% confidence interval (CI), 0.6–0.9] at 5 years, 1.7% (95% CI, 1.4–1.9) at 10 years, and 2.9% (95% CI, 2.5–3.4) at 15 years after transplantation.

Extensive-type chronic GVHD has repeatedly been shown to be a significant risk factor for the development of secondary solid tumor and is highly correlated with squamous cell carcinoma [8, 9, 12, 15, 16]. Extensive-type chronic GVHD was also shown to be a significant risk factor for oral cancer in our study. Extensive-type chronic GVHD was shown to be a significant risk factor for esophageal cancer, which was found to be increased in recipients compared with the general population in our study as well as in two other smaller Japanese cohorts in previous studies [11, 14]. Subjects were shown to be at a higher risk for the development of cancers of the oral cavity or esophagus at all time periods after 1 year. Data were not obtained for affected organ sites of chronic GVHD in JSHCT data collection prior to transplants in 2006. Therefore, we could not investigate whether oral or esophageal cancers were related to the chronic GVHD of the same organ. However, results of risk factor analyses for cancer sites of oral, esophagus, colon, and skin which showed high associations of extensive-type chronic GVHD and oral or esophagus cancer, limited-type chronic GVHD, and skin cancer showed that development of secondary solid tumors were likely to be influenced by GVHD-affected sites. Lifelong screening for oral, pharynx, or esophageal cancers for recipients with active or resolved chronic GVHD is important after 1-year post-transplant. The prognosis of solid cancers is highly influenced by the stage of the cancers when they are first detected. Our findings support recently published recommended screening guidelines [21, 22].

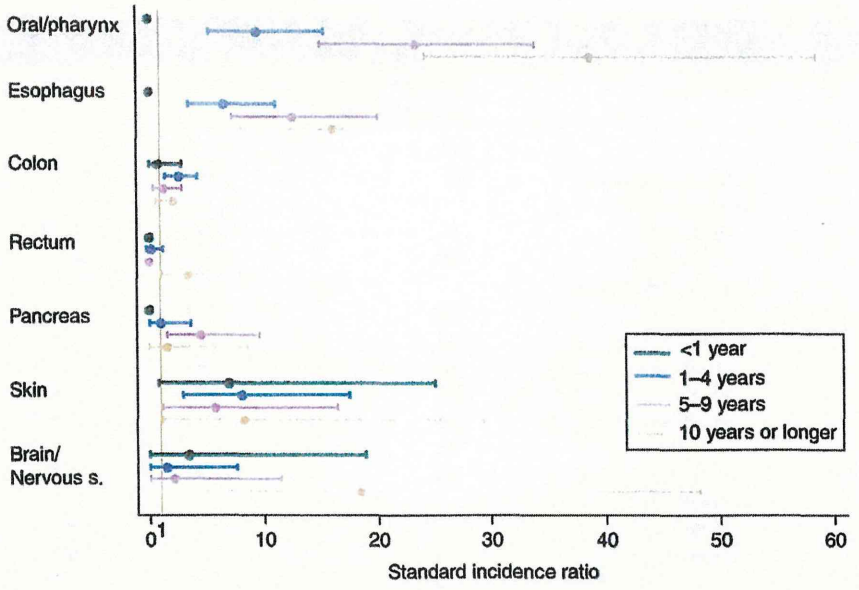


**Figure 2.** Trends of standard incidence ratios (SIRs) and its 95% confidence intervals (CIs) of high-risk secondary solid cancer sites according to time since transplant. The SIR and 95% CIs for <1, 1–4, 5–9, and 10 years or longer post-transplant were 0.0, 9.5 (5.4–15.4), 23.4 (15.4–34.0), and 38.5 (23.8–58.9) for oral/pharynx cancer, 0.0, 6.5 (3.5–11.2), 12.6 (7.3–20.2), and 16.8 (8.4–30.1) for esophageal cancer, 0.8 (0.1–2.9), 2.7 (1.5–4.3), 1.2 (0.4–2.9), and 2.2 (0.6–5.7) for colon cancer, 0.0, 0.2 (0.0–1.3), 0.0, and 3.6 (1.2–8.4) for rectum cancer, 0.0, 1.0 (0.1–3.7), 4.5 (1.6–9.7), and 1.6 (0.0–8.9) for pancreatic cancer, 7.0 (0.8–25.1), 8.1 (3.0–17.5), 5.7 (1.2–16.7), and 8.4 (1.0–30.3) for skin cancer, and 3.4 (0.1–19.0), 1.4 (0.0–7.7), 2.1 (0.1–11.6), and 19.1 (5.2–49.0) for cancers of brain/nervous system, respectively.

**Table 3.** Standard incidence ratio according to recipient's age at transplant

| | Recipient's age at transplantation | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 16–19 | | 20–29 | | 30–39 | | 40–49 | | 50–59 | | 60 or older | |
| Number-of-recipients | 1399 | | 3506 | | 3787 | | 4167 | | 3549 | | 1137 | |
| Person-years at risk | 7083 | | 17 912 | | 17 303 | | 16 198 | | 9126 | | 1843 | |
| Secondary cancer sites | O | SIR | O | SIR | O | SIR | O | SIR | O | SIR | O | SIR |
| All solid cancers | 18 | 17.0* | 28 | 4.1* | 51 | 2.4* | 71 | 1.4* | 79 | 1.5* | 22 | 1.0 |
| Oral/pharynx | 7 | 140.0* | 11 | 50.7* | 19 | 36.5* | 13 | 10.1* | 12 | 8.1* | 2 | 3.9 |
| Esophagus | 1 | 350.0* | 3 | 131.0* | 13 | 48.5* | 10 | 7.0* | 13 | 5.9* | 1 | 1.1 |
| Stomach | 1 | 13.3 | 0 | 0.0 | 1 | 0.3 | 7 | 0.8 | 5 | 0.5 | 2 | 0.5 |
| Colon | 0 | 0.0 | 0 | 0.0 | 3 | 2.0 | 6 | 1.3 | 12 | 2.1* | 6 | 2.6 |
| Rectum | 1 | 33.1 | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 | 4 | 0.9 | 0 | 0.0 |
| Liver | 1 | 66.4* | 1 | 8.1 | 0 | 0.0 | 2 | 0.8 | 3 | 0.8 | 1 | 0.6 |
| Gallbladder | 0 | 0.0 | 0 | 0.0 | 2 | 12.0* | 1 | 1.5 | 2 | 2.1 | 1 | 2.0 |
| Pancreas | 0 | 0.0 | 0 | 0.0 | 2 | 5.5 | 1 | 0.7 | 4 | 2.0 | 2 | 2.3 |
| Broncus/lung | 1 | 44.3* | 0 | 0.0 | 2 | 1.6 | 7 | 1.6 | 7 | 1.1 | 2 | 0.7 |
| Skin | 1 | 28.6 | 1 | 6.3 | 0 | 0.0 | 6 | 11.6* | 4 | 7.4* | 1 | 4.0 |
| Female breast | 0 | 0.0 | 1 | 0.7 | 1 | 0.2 | 1 | 0.1 | 3 | 0.5 | 1 | 0.9 |
| Cervix uteri | 0 | 0.0 | 1 | 1.2 | 3 | 1.9 | 2 | 1.4 | 1 | 1.4 | 0 | 0.0 |
| Corpus uteri | 0 | 0.0 | 1 | 5.2 | 0 | 0.0 | 2 | 1.4 | 2 | 1.6 | 0 | 0.0 |
| Ovary | 0 | 0.0 | 1 | 3.2 | 0 | 0.0 | 1 | 0.7 | 0 | 0.0 | 1 | 6.4 |
| Prostate | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.4 | 0 | 0.0 | 1 | 0.5 |
| Bladder | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.3 | 2 | 1.7 | 0 | 0.0 |
| Kidney | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 1.4 | 0 | 0.0 | 0 | 0.0 |
| Brain/nervous system | 2 | 23.9* | 1 | 3.8 | 1 | 2.7 | 1 | 2.0 | 1 | 2.6 | 1 | 9.1 |
| Thyroid | 0 | 0.0 | 2 | 3.9 | 0 | 0.0 | 1 | 0.7 | 1 | 0.9 | 0 | 0.0 |

*$P < 0.05$.