levels and primary tumor growth as compared to D3H2LN alone, indicating that recruited CAFs (MEFs) further contributes to the host OPN levels and tumor growth. However, mOPN plasma levels were similar between mice injected with D3H2LN cells alone or D3H2LN with OPN KO-MEFs, indicating that MEFs-derived OPN did not contribute to the increase of host-derived OPN in tumor-bearing mice. In another words, host-derived cells in tumor-bearing mice produce OPN enough to increase plasma level. More importantly, our data demonstrated that not only MEFs-derived factor(s) but also OPN are involved in primary tumor growth (Fig. 7a).

Thirdly, we provide new mechanisms about how recruitment of CAFs into tumor tissues can be regulated. It is well-known that tumor inoculation induces recruitment/appearance of CAFs [9, 26]. It has been shown that malignant tumor cells secrete OPN and that OPN activated bone marrow-derived stromal precursor cells ($Sca1^+ckit^-$ BMC) migrate into low malignant tumor tissues (indolent cells), where $Sca1^+ckit^-$ BMC activated CAFs, leading to the acquisition of malignant phenotype of indolent cells [6, 27]. However, how production of tumor-derived OPN is regulated and how recruitment/appearance of CAFs is induced in those studies has not been demonstrated. Consistent with previous reports [9, 26], tumor inoculation induced the appearance of endogenous CAFs (Fig. 5c). We demonstrate that the recruitment/appearance of FAP-positive CAFs was regulated by tumor α9β1 integrin (Fig. 5c). This finding is of importance since tumor volume and numbers of CAFs were well correlated (Fig. 5c right column). A potential mechanism for induction of soluble factor(s) by α9β1-mediated signaling might be as follows. It was previously shown that PDGF-CC could recruit CAFs [9]; however, the expression level of PDGF-CC in tumor tissues were not influenced by anti-hα9β1 antibody treatment (data not shown), indicating that PDGF-CC was not involved in the recruitment of CAFs under our experimental conditions. α9β1 integrin activates NF-κB via PI3K pathway in neutrophil [28, 29]. NF-κB, which is activated by PI3K pathway in tumor cells, induces the production of cytokines, which promote the establishment of tumor microenvironment [30]. We found that the stimulation of D3H2LN cells by Tnfn3-RAA, a recombinant fragment of TN-C, which contains the α9β1 integrin-binding site [31] or OPN-N-half induces phosphorylation of Akt (data not shown). Therefore, α9β1 integrin-mediated signaling may regulate NF-κB via PI3K pathway, and promotes the expression of soluble factor(s), that recruit(s) CAFs. We previously reported that α9β1 integrin-mediated signaling induces the production of IL-6 via MEK/ERK pathway in conventional dendritic cells [31]. Tumor-derived IL-6 activates CAFs [32]. Therefore, MEK/ERK pathway also may be involved in α9β1 integrin-mediated signaling, leading to the production of soluble factor(s), which recruit(s) CAFs.

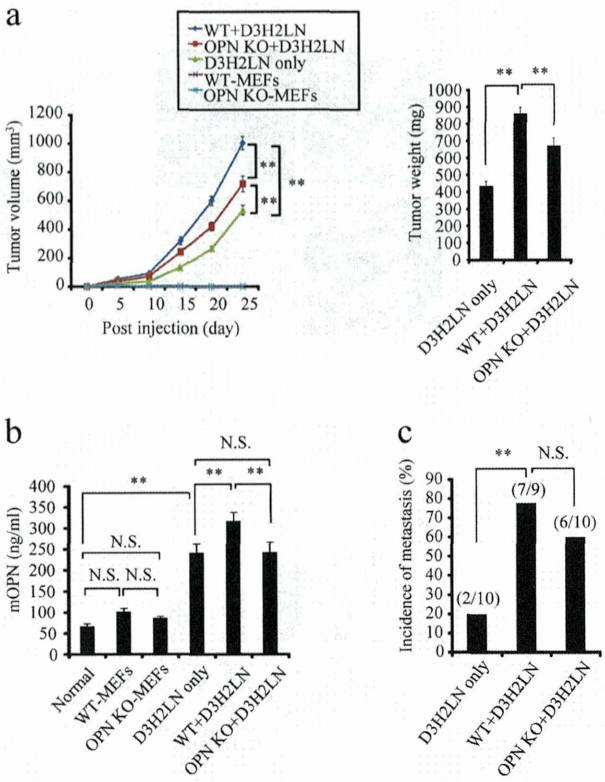


Fig. 7 CAF-derived OPN enhanced tumor growth, but not lymphatic metastasis. **a** Tumor volumes were measured up to day 25 after inoculation of D3H2LN cells (*green triangle*: $n=10$) or with either WT- (*blue rhombus*: $n=9$) or OPN KO-MEFs (*red square*: $n=10$). As negative controls, WT-(violet cross: $n=5$) or OPN KO-MEFs (*aqua blue asterisk*: $n=5$) only were inoculated (*left panel*). Tumor weights on day 25 were measured (*right panel*). *Bars* indicate mean values±SEM. **$p<0.01$, ANOVA with post test analysis (PLSD). **b** The concentration of host-derived OPN (mOPN) in plasma on day 25. D3H2LN cells alone ($n=10$), or with either WT- ($n=9$) or OPN KO-MEFs ($n=10$) were inoculated. WT- ($n=5$) or OPN KO-MEFs ($n=5$) without tumor cells were also inoculated. Plasma mOPN levels were measured by ELISA. *Bars* indicate mean values±SEM. *N.S.* No significant difference, **: $p<0.01$, ANOVA with post test analysis (PLSD). **c** The incidence of lymphatic metastasis on day 25. D3H2LN cells alone ($n=10$), or with either WT ($n=9$) or OPN KO-MEFs ($n=10$) were inoculated and metastatic lymph nodes were detected using IVIS. *N.S.* No significant difference, **: $p<0.01$, χ^2 test

Fourthly, we demonstrate that tumor α9β1 integrin was involved in lymphatic metastasis. Blockage of tumor α9β1 integrin-mediated signaling by anti-hα9β1 antibody reduced the incidence of lymphatic metastasis at day 30 after inoculation of breast cancer cells into nude mice (Fig. 4a). Although the incidence of lymphatic metastasis was comparable between control IgG and anti-hα9β1 antibody-treated groups at later time points, metastatic burden was reduced by anti-hα9β1 antibody (Fig. 4b). Of note, the proliferation rate of cancer cells in metastatic sites was not changed by anti-hα9β1 antibody (Supplementary Fig. S2). As shown in Fig. 3b, inhibition of tumor growth by anti-hα9β1 antibody was not complete. Therefore, it is likely that tumor cells which escaped

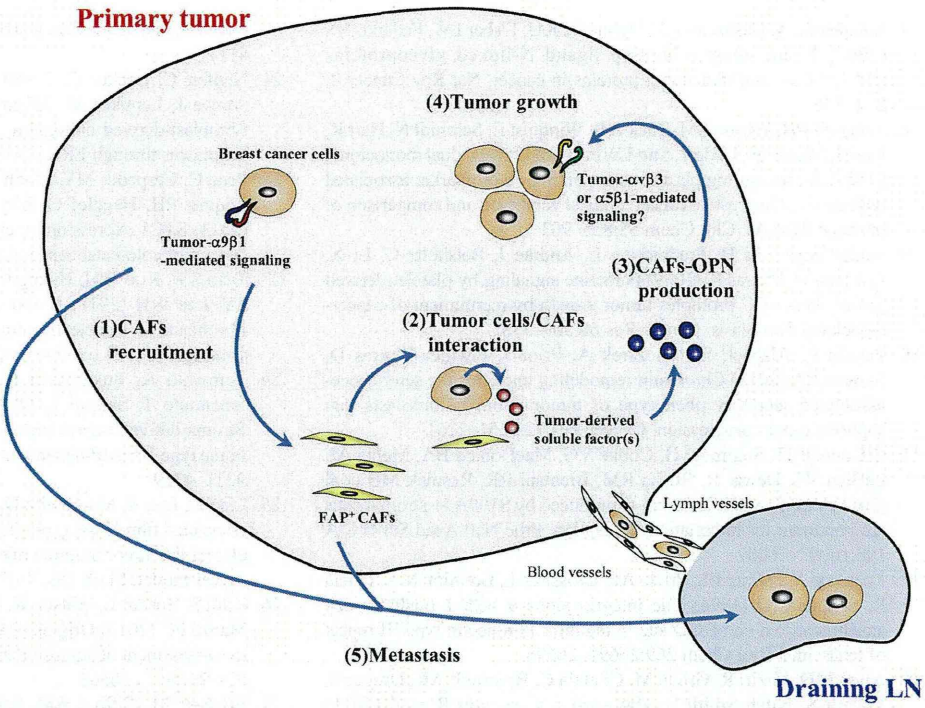


Fig. 8 The role of tumor-derived α9β1 integrin and CAF-derived OPN in tumor growth and metastasis. (*1*) Tumor-derived α9β1 integrin-mediated signaling triggers the recruitment of CAFs into the primary tumor. (*2*) In the primary tumor, tumor cells interact with CAFs through the soluble factor(s). (*3*) Then, these interactions induce the production of OPN from CAFs. (*4*) CAF-derived OPN enhances tumor growth in the primary tumor tissue. RGD-recognizing integrins, such as αvβ3 or α5β1 integrin may be involved in this process. (*5*) CAFs enhance lymphatic metastasis by OPN-independent mechanisms. The tumor-derived α9β1 integrin-mediated signaling also promotes invasion of tumor cells, thereby enhancing lymphatic metastasis

from anti-antibody treatment were responsible for tumor metastasis. In addition, CAFs are quite heterogenous cell populations [33]. Therefore, CAFs between primary and metastatic tumors might be functionally distinct. CAFs within primary tumor cells but not metastatic sites contributes to tumor growth in tumor α9β1-dependent fashion. We also found that tumor α9β1 integrin-mediated signaling regulated invasion of breast cancer cells in vitro (Fig. 2a). Thus, the reduction of metastatic burden by anti-hα9β1 antibody might be due to the impairment of cell motility.

Finally, it is of importance to discuss at which step tumor α9β1 and binding of OPN to α9β1 are involved. We found that in vitro stimulation of D3H2LN cells by full-length form of mOPN (which binds to RGD-recognizing integrin including αvβ3 and α5β1), but not N-half-RAA OPN (which expresses α9β1–binding site [10]), induced proliferation of tumor cells (data not shown). Note that D3H2LN cells express αvβ3 and α5β1 (Fig. 1c). Therefore, CAFs-derived OPN may bind to tumor-αvβ3 and α5β1 and promote tumor growth. In summary, as depicted in Fig. 8, (1) Our data demonstrate that primary tumor growth was regulated by tumor α9β1 integrin. In addition, tumor aggressiveness was also regulated by tumor α9β1 integrin. (2) The levels of host-derived OPN production were well correlated with tumor volume and number of CAFs. Host-derived OPN production was regulated by tumor α9β1 integrin. (3) Recruitment of CAFs into tumor tissues was regulated by tumor α9β1 integrin. (4) Primary tumors induce CAFs to produce OPN by through secrete soluble factor(s). (5) CAF-derived OPN was involved in primary tumor growth. Taken together, our studies suggest that tumor α9β1 integrin may be an attractive therapeutic target for breast cancer.

Acknowledgments We thank Chiemi Kimura and Orie Yamamori (Hokkaido University) for excellent technical assistance, and Tetsuro Nakamura (Gene Techono Science Corporation, Sapporo, Japan) for valuable suggestion about the use of anti-hα9β1 antibody and for valuable discussions during course of experiments. This study was supported by grant-in-aids from the Ministry of Education, Culture, Science, Sports, and Technology of Japan (21390113(B)) to Toshimitsu Uede.

Disclosure There are no potential conflicts of interest for all authors.

References

1. Chaffer CL, Weinberg RA (2011) A perspective on cancer cell metastasis. Science 331:1559–1564
2. Joyce JA, Pollard JW (2009) Microenvironmental regulation of metastasis. Nat Rev Cancer 9:239–252
3. Kalluri R, Zeisberg M (2006) Fibroblasts in cancer. Nat Rev Cancer 6:392–401
4. Uede T (2011) Osteopontin, intrinsic tissue regulator of intractable inflammatory diseases. Pathol Int 61:265–280
5. Oskarsson T, Acharyya S, Zhang XH, Vanharanta S, Tavazoie SF, Morris PG, Downey RJ, Manova-Todorova K, Brogi E, Massague J (2011) Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. Nat Med 17:867–874
6. McAllister SS, Gifford AM, Greiner AL, Kelleher SP, Saelzler MP, Ince TA, Reinhardt F, Harris LN, Hylander BL, Repasky EA et al (2008) Systemic endocrine instigation of indolent tumor growth requires osteopontin. Cell 133:994–1005

7. Bellahcene A, Castronovo V, Ogbureke KU, Fisher LW, Fedarko NS (2008) Small integrin-binding ligand N-linked glycoproteins (SIBLINGs): multifunctional proteins in cancer. Nat Rev Cancer 8: 212–226
8. Anborgh PH, Wilson SM, Tuck AB, Winquist E, Schmidt N, Hart R, Kon S, Maeda M, Uede T, Stitt LW et al (2009) New dual monoclonal ELISA for measuring plasma osteopontin as a biomarker associated with survival in prostate cancer: clinical validation and comparison of multiple ELISAs. Clin Chem 55:895–903
9. Anderberg C, Li H, Fredriksson L, Andrae J, Betsholtz C, Li X, Eriksson U, Pietras K (2009) Paracrine signaling by platelet-derived growth factor-CC promotes tumor growth by recruitment of cancer-associated fibroblasts. Cancer Res 69:369–378
10. Pazolli E, Alspach E, Milczarek A, Prior J, Piwnica-Worms D, Stewart SA (2012) Chromatin remodeling underlies the senescence-associated secretory phenotype of tumor stromal fibroblasts that supports cancer progression. Cancer Res 72:2251–2261
11. O'Connell JT, Sugimoto H, Cooke VG, MacDonald BA, Mehta AI, LeBleu VS, Dewar R, Rocha RM, Brentani RR, Resnick MB et al (2011) VEGF-A and Tenascin-C produced by S100A4+ stromal cells are important for metastatic colonization. Proc Natl Acad Sci U S A 108:16002–16007
12. Yokosaki Y, Palmer EL, Prieto AL, Crossin KL, Bourdon MA, Pytela R, Sheppard D (1994) The integrin alpha 9 beta 1 mediates cell attachment to a non-RGD site in the third fibronectin type III repeat of tenascin. J Biol Chem 269:26691–26696
13. Allen MD, Vaziri R, Green M, Chelala C, Brentnall AR, Dreger S, Vallath S, Nitch-Smith H, Hayward J, Carpenter R et al (2011) Clinical and functional significance of alpha9beta1 integrin expression in breast cancer: a novel cell-surface marker of the basal phenotype that promotes tumour cell invasion. J Pathol 223:646–658
14. Vantyghem SA, Allan AL, Postenka CO, Al-Katib W, Keeney M, Tuck AB, Chambers AF (2005) A new model for lymphatic metastasis: development of a variant of the MDA-MB-468 human breast cancer cell line that aggressively metastasizes to lymph nodes. Clin Exp Metastasis 22:351–361
15. Farnsworth RH, Lackmann M, Achen MG, Stacker SA (2013) Vascular remodeling in cancer. Oncogene. doi:10.1038/onc.2013.304
16. Vlahakis NE, Young BA, Atakilit A, Sheppard D (2005) The lymphangiogenic vascular endothelial growth factors VEGF-C and -D are ligands for the integrin alpha9beta1. J Biol Chem 280:4544–4552
17. Feng F, Rittling SR (2000) Mammary tumor development in MMTV-c-myc/MMTV-v-Ha-ras transgenic mice is unaffected by osteopontin deficiency. Breast Cancer Res Treat 63:71–79
18. Chong HC, Tan CK, Huang RL, Tan NS (2012) Matricellular proteins: a sticky affair with cancers. J Oncol 351089. doi: 10.1155/2012/351089
19. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA (2005) Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 121:335–348
20. Ijichi H, Chytil A, Gorska AE, Aakre ME, Bierie B, Tada M, Mohri D, Miyabayashi K, Asaoka Y, Maeda S et al (2011) Inhibiting Cxcr2 disrupts tumor-stromal interactions and improves survival in a mouse model of pancreatic ductal adenocarcinoma. J Clin Invest 121:4106–4117
21. Neufert C, Becker C, Tureci O, Waldner MJ, Backert I, Floh K, Atreya I, Leppkes M, Jefremow A, Vieth M et al (2013) Tumor fibroblast-derived epiregulin promotes growth of colitis-associated neoplasms through ERK. J Clin Invest 123:1428–1443
22. Pena C, Cespedes MV, Lindh MB, Kiflemariam S, Mezheyeuski A, Edqvist PH, Hagglof C, Birgisson H, Bojmar L, Jirstrom K et al (2013) STC1 expression by cancer-associated fibroblasts drives metastasis of colorectal cancer. Cancer Res 73:1287–1297
23. Tyan SW, Kuo WH, Huang CK, Pan CC, Shew JY, Chang KJ, Lee EY, Lee WH (2011) Breast cancer cells induce cancer-associated fibroblasts to secrete hepatocyte growth factor to enhance breast tumorigenesis. PLoS One 6:e15313
24. Taniwaki K, Fukamachi H, Komori K, Ohtake Y, Nonaka T, Sakamoto T, Shiomi T, Okada Y, Itoh T, Itohara S et al (2007) Stroma-derived matrix metalloproteinase (MMP)-2 promotes membrane type 1-MMP-dependent tumor growth in mice. Cancer Res 67: 4311–4319
25. Liao D, Luo Y, Markowitz D, Xiang R, Reisfeld RA (2009) Cancer associated fibroblasts promote tumor growth and metastasis by modulating the tumor immune microenvironment in a 4T1 murine breast cancer model. PLoS One 4:e7965
26. Kidd S, Spaeth E, Watson K, Burks J, Lu H, Klopp A, Andreeff M, Marini FC (2012) Origins of the tumor microenvironment: quantitative assessment of adipose-derived and bone marrow-derived stroma. PLoS One 7:e30563
27. Elkabets M, Gifford AM, Scheel C, Nilsson B, Reinhardt F, Bray MA, Carpenter AE, Jirstrom K, Magnusson K, Ebert BL et al (2011) Human tumors instigate granulin-expressing hematopoietic cells that promote malignancy by activating stromal fibroblasts in mice. J Clin Invest 121:784–799
28. Saldanha-Gama RF, Moraes JA, Mariano-Oliveira A, Coelho AL, Walsh EM, Marcinkiewicz C, Barja-Fidalgo C (2010) alpha(9)beta(1) integrin engagement inhibits neutrophil spontaneous apoptosis: involvement of Bcl-2 family members. Biochim Biophys Acta 1803:848–857
29. Ross EA, Douglas MR, Wong SH, Ross EJ, Curnow SJ, Nash GB, Rainger E, Scheel-Toellner D, Lord JM, Salmon M et al (2006) Interaction between integrin alpha9beta1 and vascular cell adhesion molecule-1 (VCAM-1) inhibits neutrophil apoptosis. Blood 107: 1178–1183
30. Hutti JE, Pfefferle AD, Russell SC, Sircar M, Perou CM, Baldwin AS (2012) Oncogenic PI3K mutations lead to NF-kappaB-dependent cytokine expression following growth factor deprivation. Cancer Res 72:3260–3269
31. Kanayama M, Morimoto J, Matsui Y, Ikesue M, Danzaki K, Kurotaki D, Ito K, Yoshida T, Uede T (2011) alpha9beta1 integrin-mediated signaling serves as an intrinsic regulator of pathogenic Th17 cell generation. J Immunol 187:5851–5864
32. Hugo HJ, Lebret S, Tomaskovic-Crook E, Ahmed N, Blick T, Newgreen DF, Thompson EW, Ackland ML (2012) Contribution of fibroblast and mast cell (afferent) and tumor (efferent) IL-6 effects within the tumor microenvironment. Cancer Microenviro Off J Int Cancer Microenviron Soc. doi:10.1007/s12307-012-0098-7
33. Sugimoto H, Mundel TM, Kieran MW, Kalluri R (2006) Identification of fibroblast heterogeneity in the tumor microenvironment. Cancer Biol Ther 5:1640–1646

Int J Clin Oncol (2014) 19:771–778
DOI 10.1007/s10147-014-0715-1

ORIGINAL ARTICLE

Questionnaire survey for the development and publication of cancer clinical practice guidelines in Japan

Tomohisa Furuhata · Koichi Hirata · Fumihiko Wakao · Kenji Okita · Masafumi Imamura · Yoshihiko Maehara · Masahiko Nishiyama

Received: 28 March 2014 / Accepted: 23 May 2014 / Published online: 26 June 2014

Abstract
Purpose To understand the current situation of the development and publication of cancer clinical practice guidelines and discuss an ideal structure in future.
Methods A questionnaire survey pertaining to the development and publication of cancer clinical practice guidelines was conducted with funding by a Health and Labour Sciences Research Grant. Respondents included presidents and chairpersons of academic societies developing guidelines and members of the Cancer Guidelines Committee of the Japan Society of Clinical Oncology who were specialists in various cancer sites.
Results Concerning the question of funding for the development and publication of the guidelines, 80.7 % of respondents indicated that partial public funding is required. As for the flow of public funds, 80.4 % of respondents thought that funds should be distributed appropriately to each academic society by a third-party organization. Regarding the question about the publication of the guidelines, 82.5 % of respondents replied that a comprehensive publication site needs to be established. In terms of the choice of organization that would be responsible for setting up and managing this site, the responses varied as follows: "a newly established organization" (38.3 %); "Center for Cancer Control and Information Services" (29.8 %); "Japan Society of Clinical Oncology" (23.4 %); and "Medical Information Network Distribution Service" (23.4 %) (multiple answers allowed).
Conclusion While the guidelines should be developed voluntarily by each academic society, partial public funding is also considered to be necessary for maintaining the continuous revision process. As for the publication of the guidelines, the establishment of a new comprehensive publication site would improve user convenience.

Keywords Clinical Practice Guidelines (CPG) · Center for Cancer Control and Information Services · Japan Society of Clinical Oncology (JSCO) · Medical Information Network Distribution Service (MINDS) · Cancer Control Act

T. Furuhata (✉) · K. Hirata · K. Okita · M. Imamura
Department of Surgery, Surgical Oncology and Science, Sapporo Medical University, South 1 West 16, Chuo-ku, Sapporo 060-8543, Japan
e-mail: furuhata@sapmed.ac.jp

F. Wakao
National Cancer Center, Center for Cancer Control and Information Services, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

M. Nishiyama
Department of Molecular Pharmacology and Oncology, Gunma University Graduate School of Medicine, 3-39-22, Showa-Machi, Maebashi, Gunma 371-8511, Japan

Introduction

The Basic Plan to Promote Cancer Control Programs was established in accordance with the Cancer Control Act of 2006. This plan states that it supports the development and revision of cancer clinical practice guidelines (CPG). CPG maintenance is an important issue as one of the objectives of national policy. The Gastric Cancer Treatment Guidelines published in 2001 paved the way for subsequent cancer CPG in Japan. Many CPG have since been published, supported

by public research funds and the efforts of the academic societies. Each academic society develops guidelines to a high academic standard. They voluntarily engage in the development of the guidelines as a social contribution, recognizing that this is one of their missions. However, ongoing revision of the guidelines burdens academic societies financially and administratively, especially societies with a small membership and those dealing with rare cancers. Along with publishing printed guidelines, academic societies post their guidelines on their websites. Furthermore, they provide guidelines to organizations such as the Japan Society of Clinical Oncology (JSCO) and the Medical Information Network Distribution Service (MINDS). However, the guidelines are not all provided to both JSCO and Minds; as a result, when a user searches JSCO or MINDS for a guideline, it is not always found. In addition to this user inconvenience, the problem of inconsistent updates has been pointed out as a factor that may be confusing users.

The National Comprehensive Cancer Network (NCCN) Guidelines is regarded as one of the most valuable and credible cancer guidelines in Japan. Reasons for the popularity of the NCCN guidelines include: (1) frequent revisions and constant updates that maintain a latest-version status; (2) ease of browsing owing to the standard format; and (3) ease of access to various guidelines. These advantages are enabled by the well-established infrastructure of the NCCN, which consists of the Guidelines Steering Committee, Guidelines Panels, and Guidelines Staff. The Guidelines Steering Committee is in charge of spearheading and coordinating the overall direction, the Guidelines Panels develop the guidelines, and the Guidelines Staff attend to administrative tasks. Such a division of labour in NCCN brings a gain in efficiency [1]. This infrastructure has been regarded as an exemplary model for Japan's cancer CPG project and is a matter requiring immediate attention.

Thus, a questionnaire survey was conducted to assess the current situation of the development and publication of cancer CPG with funding by Health and Labour Sciences Research Grant. Based on the results of the survey, we intend to propose a new organizational structure that will facilitate the future development and publication of cancer CPG in Japan.

Subjects and methods

A questionnaire survey pertaining to the development and publication of cancer CPG was conducted with funding by Health and Labour Sciences Research Grant. A total of 57 cancer CPG experts participated in the survey; specifically, 23 presidents or chairpersons from academic societies which develop cancer CPG and 24 field representatives in JSCO's Cancer Guidelines Committee. The latter 24 are nominated by each academic society. The questionnaire was composed of 20 questions regarding the following: (1) progress status; (2) desirable financial support; and (3) organizational structure for developing and publishing cancer CPG

Table 1 Contents of questionnaire survey pertaining to the development and publication of cancer CPG

No.	Questions
1	What is the scope of your responsibility vis-à-vis your responses to this questionnaire?
2	How many individuals or facilities does your academic society consist of?
3	Please describe the committee that developed your cancer CPG and provide the number of committee members
4	Please describe the budget required for cancer CPG development and management in your academic society
5	What progress have you made toward releasing a printed cancer CPG publication?
6	What progress have you made toward making your cancer CPG publication available on the Internet?
7	Please describe the current content of recommendations when developing cancer CPG
8	Please describe the method used to determine the level of recommendation in cancer CPG
9	Please describe the amounts and sources of funds for development of the first edition cancer CPG
10	Which is the desirable financial support for the development and publication of the cancer CPG (multiple answers allowed)?
11	Please describe how you manage funds for use in developing cancer CPG?
12	Which would be the desirable flow of public research funds (multiple answers allowed)?
13	Which would be an appropriate third-party organization for distribution of public research funds (multiple answers allowed)?
14	What types of work, if any, would you want to outsource to others when developing cancer CPG?
15	What kinds of support, if any, do you think organizations developing cancer CPG for the first time, or even organizations with practical experience in developing cancer CPG, require?
16	Do you think that a comprehensive publication site of cancer CPG such as NCCN is necessary?
17	Where should a comprehensive publication site of cancer CPG be set up (multiple answers allowed)?
18	What do you require to provide cancer CPG for the comprehensive publication site (multiple answers allowed)?
19	What problems do you anticipate in developing cancer CPG in the future? (multiple answers allowed)
20	If an organization were to be newly established in order to facilitate collaboration among academic parties dealing in cancer CPG, would your academic society participate in it?

CPG Clinical Practice Guidelines

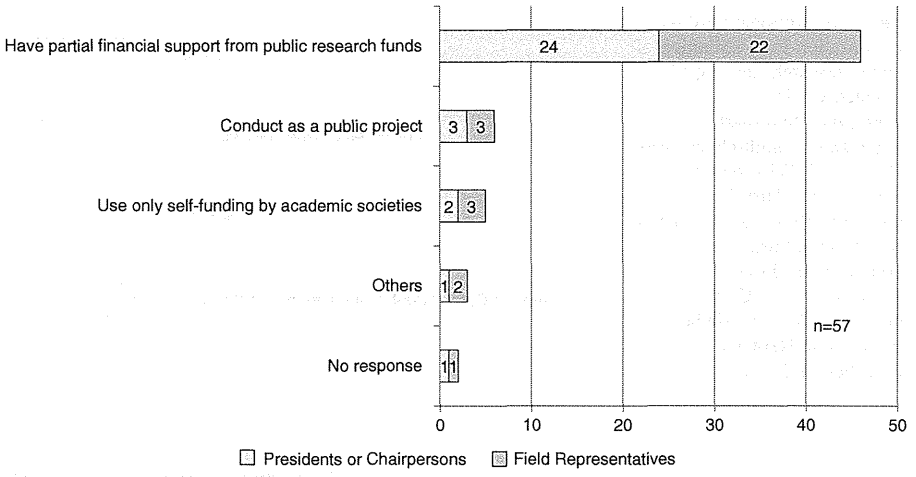


Fig. 1 Financial support for the development and publication of the cancer CPG. Q10: "Which is the desirable financial support for the development and publication of the cancer CPG (multiple answers allowed)?"

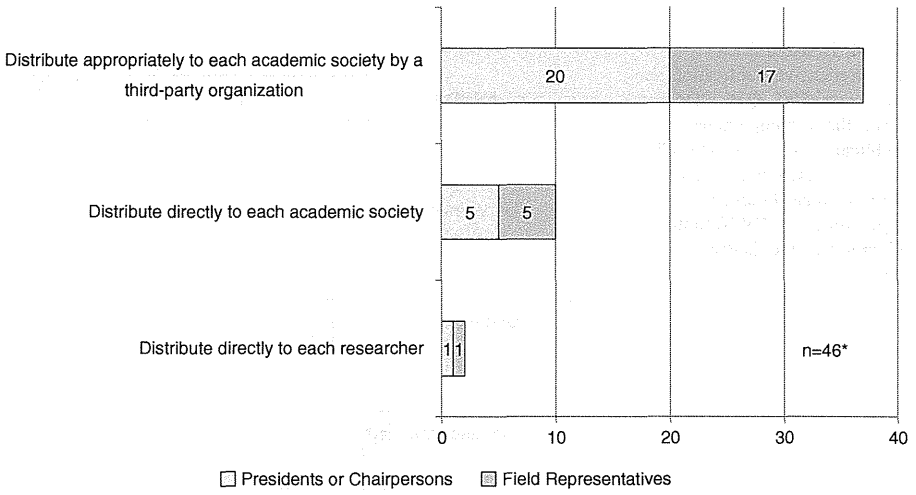


Fig. 2 Desirable flow of public research funds. Q12: "Which would be the desirable flow of public research funds (multiple answers allowed)?" *46 respondents who replied "Have partial financial support from public research funds" in Q10

(Table 1). The response rate for the questionnaire was 100 %. In this paper, we discuss the survey results with regard to desirable financial support and organizational structure for developing and publishing the cancer CPG.

Results

Financial support from public research funds

Regarding the question of funds for the development and publication of the guidelines, the most frequent response (80.7 %) was "Have partial financial support from public research funds" (Fig. 1). Other responses included "Conduct as a public project" (10.5 %) and "Use only self-funding by academic societies" (8.8 %) (Fig. 1). Concerning the desirable flow of public research funds, "Distribute appropriately to each academic society by a third-party organization" was the most frequent response (80.4 %). Other responses included the following: "Distribute directly to each academic society" (21.7 %) and "Distribute directly to each researcher" (4.3 %) (Fig. 2). As for an appropriate third-party organization, the responses were as follows: "JSCO" (54.1 %); "A newly established organization" (43.2 %); "MINDS" (21.6 %); and "Center for Cancer Control and Information Services" (8.1 %) (Fig. 3).

Comprehensive publication site for the cancer CPG

Concerning the demand for a comprehensive publication site for the cancer CPG such as NCCN, 82.5 % of the respondents replied "Necessary" (Fig. 4). In terms of where a comprehensive publication site is set up, responses

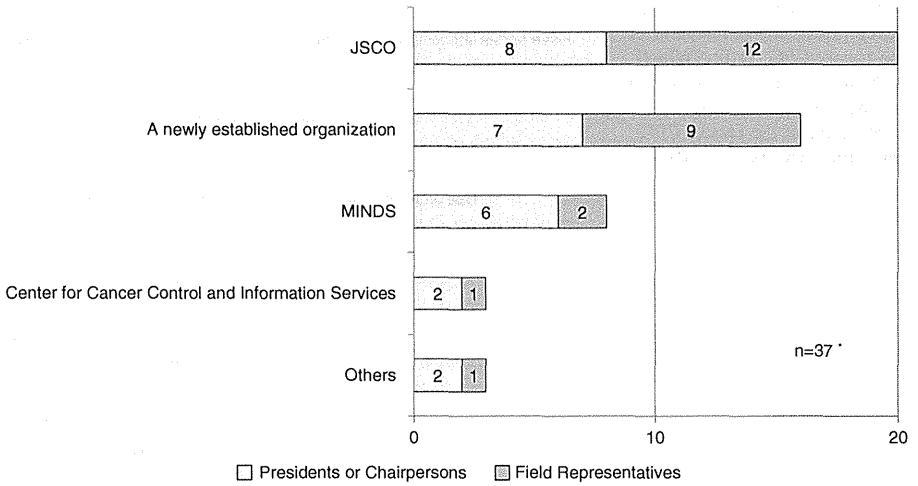


Fig. 3 Appropriate third-party organization for distribution of public research funds. Q13: "Which would be an appropriate third-party organization (multiple answers allowed)?" *37 respondents who replied "Distribute appropriately to each academic society by a third-party organization" in Q12. *JSCO* Japan Society of Clinical Oncology, *MINDS* Medical Information Network Distribution Service

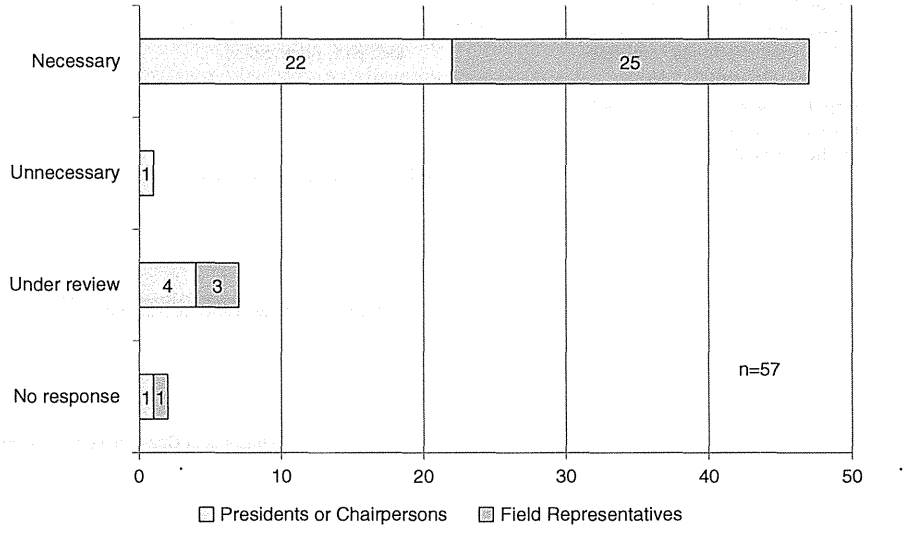


Fig. 4 Demand for a comprehensive publication site of cancer CPG. Q16: "Do you think that a comprehensive publication site of cancer CPG such as NCCN is necessary?" *CPG* Clinical Practice Guidelines, *NCCN* National Comprehensive Cancer Network

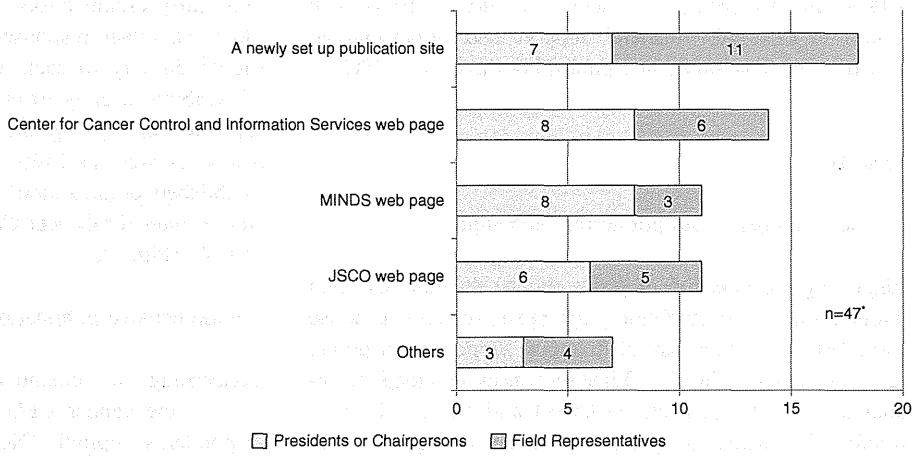


Fig. 5 Appropriate web site to exhibit cancer CPG comprehensively. Q17: "Where should a comprehensive publication site of cancer CPG be set up (multiple answers allowed)?" *47 respondents who replied that it was "necessary" for a comprehensive guidelines publication site in Q16. *JSCO* Japan Society of Clinical Oncology, *MINDS* Medical Information Network Distribution Service

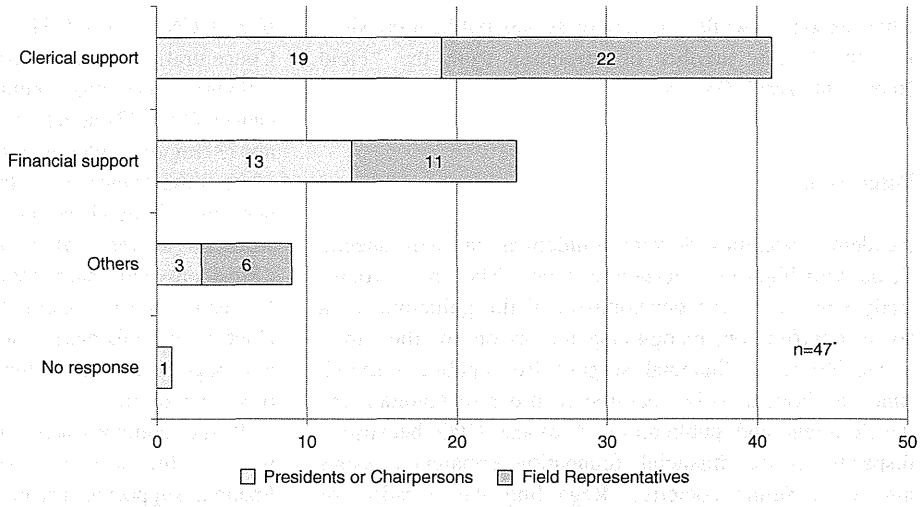


Fig. 6 Requirements for providing cancer CPG for the comprehensive publication site. Q18: "What do you require to provide cancer CPG for the comprehensive publication site (multiple answers allowed)?" *47 respondents who replied that it was "necessary" for a comprehensive publication site in Q16

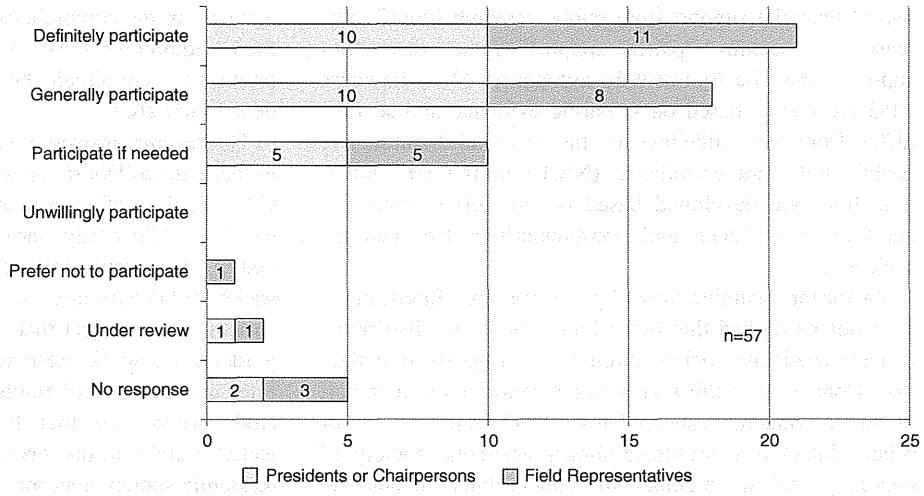


Fig. 7 Participation in a newly established organization for collaboration among academic parties. Q20: "If an organization were to be newly established in order to facilitate collaboration among academic parties dealing in cancer CPG, would your academic society participate in it?"

were as follows: "A newly set-up publication site" (38.3 %); "Center for Cancer Control and Information Services web page" (29.8 %); and "MINDS web page" and "JSCO web page" (both 23.4 %) (Fig. 5). Requirements for providing guidelines to the comprehensive publication site were "Clerical support" (87.2 %) and "Financial support" (51.1 %) (Fig. 6).

Participation in an organization for collaboration among academic parties

We have thought all along that a new organization needs to be established in order to facilitate collaboration among parties involved in cancer CPG. With regard to participation in a newly established organization, the responses were as follows: "Definitely participate" (36.8 %); "Generally participate" (31.6 %); "Participate if needed" (17.5 %); "Unwillingly participate" (0 %); and "Prefer not to participate" (1.8 %) (Fig. 7).

Dissociation of responses between "Presidents or Chairpersons" and "Field Representatives"

A large dissociation was not observed between the responses from "Presidents or Chairpersons" and "Field Representatives". However, there were slight differences in responses to questions 13 and 17. For question 13, the number of responses for "JSCO", "a newly established organization" and "MINDS" was almost the same from "Presidents or Chairpersons", while "JSCO" had the largest number of responses from the "Field Representatives" (Fig. 3). For question 17, the number of responses for "A newly set-up publication site", "Center for Cancer Control and Information Services web page" and "MINDS web page" were almost the same from "Presidents or

Chairpersons", while "A newly set-up publication site" had the largest number of responses from the "Field Representatives" (Fig. 5).

Discussion

Academic societies develop guidelines in their special fields with high-level academic policy. They have voluntarily engaged in the development of the guidelines as a social contribution, recognizing this as one of their missions. However, financial support from public research funds is thought to be required in order to maintain the development and publication of cancer CPG because a disparity in the financial foundation apparently exists among academic societies. Regarding the question of financial support, 80.7 % of respondents indicated "Have partial financial support from public research funds". The reason for seeking "partial support" rather than "full support" may be to maintain autonomy. Most Japanese CPG are purely based on scientific evidence and so they differ from the guidelines of the National Institute for Health and Care Excellence (NICE) in the UK. NICE guidelines are developed based on cost–effectiveness in addition to evidence and consequently reflect national policies [2].

As for the desirable flow of public research funds, many respondents replied that those funds should be distributed to each academic society through a third-party organization. Concerning a third-party organization, more than half of the respondents answered that JSCO would be appropriate. JSCO is a multidisciplinary academic society of oncology and its membership concurrently belongs to many specialized societies for various cancers. In 2006–2007, JSCO participated in a research program funded by the Health and Labour Sciences Research Grant as the secretariat for developing and publishing guidelines for seven sites of cancers. Subsequently, JSCO has collaborated with various academic societies, and the JSCO Cancer Guidelines Evaluation Committee has evaluated guidelines submitted from these societies [3]. Through this experience, JSCO has become familiar with the inner workings of each academic society and possesses comprehensive coordination skills. These JSCO characteristics may be the reason respondents suggested JSCO as a suitable third-party organization to distribute public research funds. Another reason may be that JSCO, unlike MINDS and the Center for Cancer Control and Information Services, is a purely academic organization and independent of national policies.

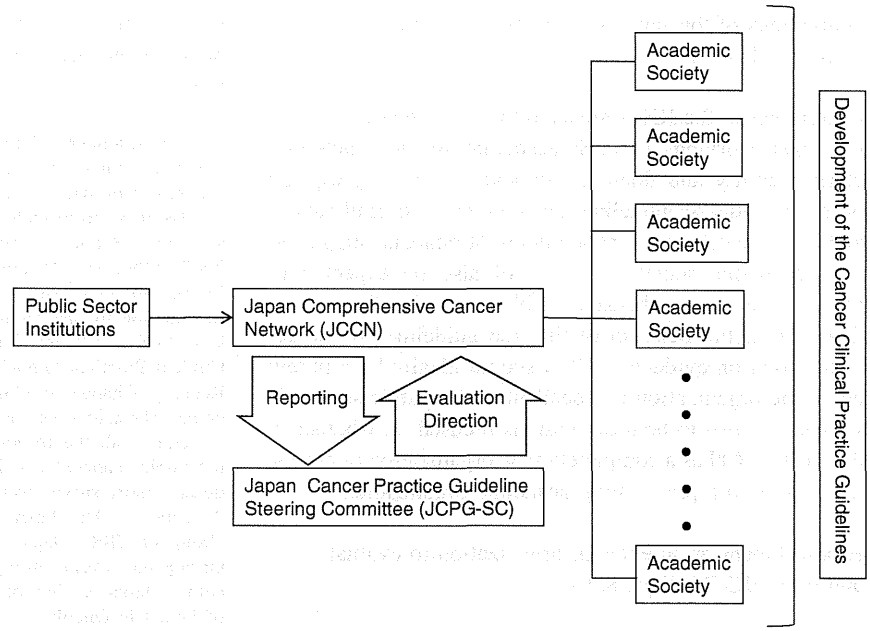
As for the publication of cancer CPG, over 80 % of respondents selected "Necessary" for a comprehensive site like NCCN, where CPG for various cancers are consolidated. Concentrating all cancer CPG at one site can accomplish the following: (1) improvement of the convenience of access for cancer CPG; (2) standardization of the guideline formats; and (3) regular updating of cancer CPG. As for the setting up of the comprehensive site, the highest number of respondents answered "A newly set-up publication site"; however, there were no answers which reached 50 %. Limited to the "Presidents and Chairpersons", the numbers of responses for "A newly set-up publication site", "Center for Cancer Control and Information Services web page" and "MINDS web page" were almost the same. At this time, opinions are obviously divided.

If the comprehensive publication site is established, most of the academic societies will need clerical and financial support as a requirement for providing guidelines. Consequently, the organization responsible for the management of the comprehensive publication site has to meet these requirements. We have to arrange where the comprehensive site should be set up to take account of the description above.

Concerning answers for participation in an organization to facilitate collaboration among parties involved in cancer CPG, 86.0 % of respondents replied "Definitely participate" or "Generally participate" or "Participate if needed". This result may reflect the fact that academic societies: (1) currently face difficulty in grasping the entire structure of a project that aims to develop and publish the guidelines; and (2) need regulations for providing guidelines and the flow of funds. Based on our findings in this study, we propose that the public research funds be collected initially in one organization and distributed to each academic society appropriately, and then that the societies provide their guidelines for a comprehensive publication site. Additionally, the establishment of a new external organization is desired in order to facilitate collaboration among the various parties. We suggest the flow of public funds and process for providing guidelines shown in Figs. 8 and 9. In this paper, we call the organization responsible for collecting both public research funds and guidelines the "Japan Comprehensive Cancer Network (JCCN)" and the external organization responsible for facilitating collaboration among the various parties the "Japan Cancer Clinical Practice Guideline Steering Committee (JCPG-SC)". An overview of the details follows:

Appropriate collection and distribution of public research funds (Fig. 8)

To distribute financial support in the right amount and at the right time, it is necessary to grasp the progress status of development, updating, and publication of guidelines for



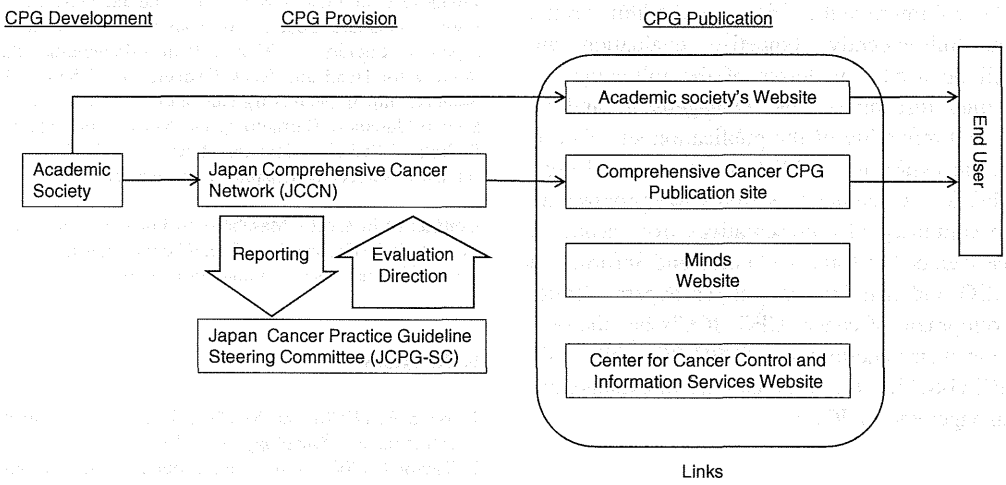


Fig. 8 Flow of public research funds for developing cancer clinical practice guidelines

Fig. 9 Flow of cancer clinical practice guidelines from academic society to end users

each type of cancer while understanding the inner workings of each individual academic society. Public research funds have been distributed for guidelines for each type of cancer directly from the public sector but this may not be ideally efficient because public sector institutions need to keep track of the progress status in the development of each guideline every fiscal year. Moreover, academic societies have to handle the administrative process themselves. We believe that the ideal structure would be to collect public research funds at JCCN and subsequently distribute them to each academic society, considering the current state of guideline development. This structure will allow each academic society to receive the right amount of funds at the right time.

Concentration of guidelines and consolidation of the publication site (Fig. 9)

Many guidelines for various types of cancers are posted on the JSCO and MINDS websites. However, theses web sites cannot be called comprehensive sites because neither JSCO or MINDS website has all-cancer CPG. Furthermore, the irregular updating of cancer CPG may cause confusion for the end users. Therefore, the most effective action is to amalgamate the latest version of all-cancer CPG and consolidate the publication site into JCCN. This will allow the establishment of a convenient and highly reliable comprehensive publication site for cancer CPG.