

Discussion

The Discussion is for discussing your results - not for introducing the field

Typical 'Discussion' flow chart

First paragraph:

Synopsis of New Findings

2nd paragraph:

General Findings

Fit/non-fit with the literature and conclusion

3rd/4th ... paragraphs:

Specific Findings

Fit/non-fit with the literature and conclusion

Strengths or weaknesses of your study

Final paragraph:

Overall conclusion and future work

Agreement then disagreement – same then different systems

Risk of Stroke in Relation to Level of Blood Pressure and Other Risk Factors in Treated Hypertensive Patients

Discussion

In the present study mean BP for the 12 months before the onset of stroke in treated hypertensive patients was not significantly different from that in treated hypertensive patients without stroke. In subjects aged <70 years, however, the mean systolic BP was significantly higher in patients with than in those without stroke. The stroke group had a higher incidence of diabetes mellitus, proteinuria, and atrial fibrillation than the control group. These results suggested that higher BP (particularly for patients aged <70 years) and the presence of cardiovascular risk factors other than hypertension and target organ damage increase the risk of first stroke in treated hypertensive patients.

Hypertension is the most powerful risk factor for stroke (Ref), and antihypertensive treatment effectively reduces the risk of stroke in hypertensive patients (Ref). Detection and treatment of hypertension are routinely performed, and the age-adjusted mortality risk for stroke has decreased markedly in many countries, including Japan (Ref). However, the efficiency of hypertension treatment still seems insufficient. According to the 1991–1994 US National Health and Nutrition Examination Survey, the percentages for treatment and control (<140/90 mm Hg) of hypertension were 54% and 27%, respectively (Ref). In the 1992 Japanese National Nutrition Survey, in which normotensive subjects were included, mean BP in the group aged 60 to 69 years was 146/85 mm Hg for men and 144/83 mm Hg for women (Ref). A cooperative study including our institute showed that mean BP was 143/81 mm Hg in treated hypertensive patients aged 50 years (Ref).

Mean BP before the onset of stroke was higher and the proportion of subjects with systolic BP >160 mm Hg was greater in the stroke group than in the control group in our patients aged <70 years old. Du et al (Ref) also showed that the risk of stroke increases with the

level of BP in treated hypertensive patients. They suggested that control of BP to <150/90 mm Hg is required for optimal stroke prevention. In the Hypertension Optimal Treatment (HOT) study, the lowest incidence of stroke occurred at a mean achieved systolic BP of 142 mm Hg, while the level of diastolic BP did not predict the onset of stroke (Ref). The lowest incidence of major cardiovascular events occurred at 139/83 mm Hg in this trial. Taken together, more strict control of BP may be beneficial to prevent the first stroke in hypertensive subjects, especially in relatively young patients.

In our study, however, the level of mean BP before the onset of stroke was not significantly different from the mean BP in the control group in all subjects or in subjects aged 70 years. The relative risk of stroke in hypertensive subjects decreases with age, although the absolute risk for stroke is high in elderly hypertensive subjects (Ref). In the Hisayama Study, the relative risk for stroke mortality was 10-fold higher in hypertensive subjects aged <60 years than normotensive subjects of similar age, but it was 3-fold higher in hypertensive subjects aged 60 years (Ref). The mean age of our patients was 71 years, which was higher than that in other studies investigating the risk of higher BP for stroke (Ref). In addition, all patients in our study were treated at a single hospital by specialists. Few patients had very high BP under treatment, and the mean systolic BP in the stroke group was <150 mm Hg. These factors may account for the lack of significant differences in treated BP between the stroke and control groups in all subjects.

Our results do not mean that hypertension control is not important for patients aged 70 years. Several intervention studies have shown that treatment of hypertension effectively reduces stroke mortality and morbidity in the elderly (Ref). The cutoff point of age 70 years in our study was arbitrary, although it was close to the mean age of study subjects. The sample size of stroke cases and controls may not be large enough to draw definite conclusions. However, we observed similar results when the size of the control group was increased by the addition of 94 patients with similar distribution of age from our previous study (Ref).

A J-shaped relationship was reported between the level of BP (especially diastolic BP) and

incidence of myocardial infarction (Ref), suggesting that low diastolic BP may be a risk for subsequent cardiovascular disease. We also observed that low diastolic BP was associated with increased recurrence of stroke or myocardial infarction (Ref). However, the proportion of patients whose BP values were in the lowest range (<130/80 mm Hg) was not different between the stroke and control groups in the present study. Several intervention trials have failed to observe the J-curve phenomenon between the level of treated BP and the incidence of stroke or myocardial infarction in hypertensive subjects, including patients with isolated systolic hypertension. (Ref) These results indicated that low BP does not increase the risk of first stroke in treated hypertensive patients, although rapid and exaggerated reduction of BP may be harmful (Ref).

In the present study BP was measured monthly, and we used mean BP over a period of 12 months for analysis. It has been shown that mean BP from repeated measurements is more predictive than casual BP for stroke occurrence (Ref). On the other hand, acute changes in BP may trigger the onset of stroke. It was reported that the variability of BP was associated with subsequent incidence of coronary heart disease (Ref). If the nearest BP obtained before the onset of stroke is different from previous values, it would be helpful to identify high-risk patients. However, the level of BP within 1 month before stroke was not significantly different from the 12-month mean in our study. The onset of stroke does not appear to be predictable from recent changes in monthly measured BP.

With regarding to stroke subtype, patients with brain hemorrhage had higher diastolic BP before the onset of stroke than those with other subtypes. Mean systolic BP was relatively high in patients with lacunar brain infarction, and this group had significantly higher systolic BP than the control group. Since brain hemorrhage and lacunar infarction are more closely related to hypertension than other subtypes (Ref), strict control of BP would be required for their prevention.

Various antihypertensive agents may have different effects on brain vasculature and circulation. Although antihypertensive treatment has been shown to reduce the risk of stroke, the relative efficacy of these drugs in the prevention of stroke has not been clarified. In the present study, calcium channel blockers were most frequently used in both stroke and control groups, as in other institutes in Japan (Ref). There were no significant differences in the use of each class of antihypertensive agent or in the proportion of patients on multiple drug regimens between the 2 groups.

In the present study the stroke group had a higher prevalence of cardiovascular risk factors and organ damage such as diabetes, proteinuria, and atrial fibrillation than the control group. The level of HDL cholesterol tended to be lower in the stroke group. Since these factors have been shown to be predictive of stroke (Ref), their presence may increase the risk of stroke in treated hypertensive patients even though BP is controlled. Early detection and treatment of risk factors are important for the effective prevention of stroke. In particular, strict control of BP appears to be beneficial for hypertensive patients with diabetes (Ref).

The use of anticoagulant and antiplatelet agents was more frequent in the stroke group than in the control group. This may have been reflected by the high prevalence of atrial fibrillation and other cardiovascular complications in the stroke group. Similar results were observed regarding the use of aspirin in the Cardiovascular Health Study (Ref). It has been shown that warfarin prevents stroke in patients with atrial fibrillation (Ref). However, there is no evidence of primary prevention of stroke with aspirin (Ref). In the HOT study, low-dose aspirin failed to prevent stroke in hypertensive patients, although it reduced myocardial infarction by 36% (Ref). The use of antiplatelet agents may not be effective in the primary prevention of stroke in treated hypertensive patients.

In conclusion, the onset of first stroke in subjects under antihypertensive treatment was related to higher levels of BP in relatively young patients but not in older patients. The risk of stroke was associated with the presence of metabolic risk factors and cardiovascular complications in those patients. Our study supported the importance of control of BP and

other risk factors for the prevention of stroke in treated hypertensive patients. Early detection and treatment of these risk factors before the development of target organ damage are strongly recommended.

Spatial and Temporal Clustering of Dengue Virus Transmission in Thai Villages

Although focal DENV transmission has been noted previously (Ref), to our knowledge this is the first study to demonstrate, using control clusters and precise human and entomological data, recent DENV transmission that was focal through space and over a short time span (15 d). DENV-infected hosts (27 enrollees) and vectors (eight *Ae. aegypti*) were exclusively identified in the 12 dengue-positive clusters, despite a nearly 1:2 ratio of enrollees between positive and negative clusters. Furthermore, we observed significant central clustering of DENV cases within positive clusters.

We suspect that focal transmission was associated with recent DENV introductions because of the 217 paired serologic specimens from positive cluster enrollees, only one revealed an elevated but declining immunoglobulin M level, which would be indicative of a recent DENV infection occurring up to 60 d prior to cluster initiation (Ref). Consequently, we attributed the observed DENV transmission (enrollees with viremia on day 0 or 15 and/or seroconversion between days 0 and 15) to recent virus introductions. This conclusion is in contrast, however, to data published by Beckett and others [20] who conducted cluster investigations in West Jakarta, Indonesia. They detected 175 recent DENV infections upon enrollment in 53 positive clusters compared to our one in 12 positive clusters, arguing against recent virus introduction. We attribute these contrasting results to study design differences. First, we recruited from schools whereas Beckett recruited from a hospital, potentially after the virus had undergone significant community-based amplification. Second, we preferentially enrolled children as the primary susceptible and amplifying

portion of the host population. Beckett additionally enrolled adults. Adults may have exhibited greater background dengue immunity that may have confounded the serologic data. Third, Beckett's study was conducted in an urban area, in contrast to rural villages in our study. Differences in transmission dynamics between these kinds of habitats were likely shaped by the frequency of DENV introductions and diversity in human behaviors.

Previous studies have documented hyperendemicity of all four DENV serotypes with an approximate 5% annual risk of acquiring an infection in KPP (Ref). In our study, cluster number 4 had a 52% attack rate among enrollees sampled during the 15-d follow-up period. However, after excluding this cluster and its matched negative cluster, the adjusted AR remained high (six per 100). This number represented a 12.4% risk of an enrolled child acquiring a DENV infection within a 15-d period when living within 100 m of a child ill with dengue. Eleven of 12 positive clusters had at least one enrollee with acute dengue in addition to the index case. Given the required intrinsic incubation period, and the finding that all eight virus isolates from mosquitoes matched the serotype recovered from the index case suggest, though not definitively, that except for children from whom virus was recovered on day 15, multiple viremic children within a cluster were infected by one or very few infected mosquitoes. Other evidence within our study to further support village- and not school-based vector sources of DENV infection are that: (1) mosquito populations in schools were extremely low, (2) children seroconverting to dengue within a cluster attended different classrooms within the school, (3) genomic sequences of the envelope (E)-regions of the viruses isolated from children and mosquitoes within the same villages were identical (R.G. Jarman, unpublished data), and (4) housemates of dengue seroconverters had a higher relative risk for DENV infection than those of nondengue seroconverters. The latter observation is consistent with previous reports (Ref). We suspect that the predominance of DENV transmission in KPP villages reflects, at least in part, routine and effective vector control in schools (insecticide every May and July and Temephos to containers every 3 mo), but not in village homes.

Differences in transmission observed between positive and negative clusters could not be attributed to differences in enrollee demographics. Differences in behavioral factors,

however, could not be excluded. Within positive clusters, risk of infection decreased with age for males and increased with age for females. This observation merits further investigation with a larger sample and analysis of sex-specific behaviors that might modify risk of infection with advancing age.

The only statistically significant determinant among environmental features associated with focal DENV transmission was the greater availability of piped water in negative clusters. Though one may consider a causal relationship (that is, less piped water availability leading to greater need for water storage leading to more containers for larval mosquito development resulting in higher dengue risk), we found no difference in the number of containers between cluster types. Although accurate data on water turn-over are difficult to obtain, the greater number of positive containers in positive than in negative clusters could not be explained by a difference in the frequency of container turn-over rates that we measured. These data could reflect a historical norm or behavior in response to lack of reliability of piped water possibly guided by people's knowledge of dengue preventive measures (Ref).

The only statistically significant difference among entomological indices was the greater number of *Ae. aegypti* pupae per person in positive than negative clusters. It is important to note that observed mean pupae per person exceed by an order of magnitude the minimum entomological threshold estimated by Focks and others [34] for a different region of Thailand. This implies that even when pupal densities are relatively high, differences in this measure of entomological risk can be epidemiologically informative. Although adult mosquito population density tended to be higher in positive clusters, differences were not statistically significant, perhaps due to limitations in sampling adult *Ae. aegypti* with backpack aspirators. Alternatively, mosquito density may be most informative when viewed in concert with herd immunity, and mosquito density alone may be less relevant than the presence of DENV-infected mosquitoes that potentially can transmit virus to multiple individuals [2,3]. Dengue cases in enrollees occurred over a wide range of female *Ae. aegypti* densities (Figure 4). At densities higher than approximately 1.5 *Ae. aegypti* females

per child, clusters were more likely to be positive than negative. This indicates that DENV transmission was more likely to occur at higher vector densities.

Perifocal spraying is a common approach by health departments to contain/control dengue. However, this practice has been found to be ineffective in aborting DENV transmission (Ref). Our data suggest that if school-based surveillance can be bolstered by rapid, easy-to-use, and affordable diagnostics, spatially and temporally focused vector control in rural areas such as KPP could be more effectively applied to contain new virus introductions and offset the theoretical risk of longitudinal transmission within and beyond village foci. Although the risk of infection decreased significantly with distance from the center of a cluster, we did not examine people living beyond 100 m of an index case. Our study did not define the spatial dimensions of DENV transmission. Nevertheless, we expect that interventions will need to go beyond a 100 m radius of the home of a DENV-infected child because viremic residents or visitors bitten by an infected mosquito can move virus farther than a flying, infected adult female *Ae. aegypti* [13,35].

We do not know the longitudinal effects of killing adult mosquitoes on transmission within a community. Koenraadt and others (Ref) determined in our study area that within 1 wk of spraying insecticide inside homes, approximately 50% of prespraying levels of *Ae. aegypti* populations were reestablished. Identifying only two of 217 child enrollees with dengue viremia on day 15, both approximately 50 m from the index case within the same positive cluster, indicates that vector control can be locally successful when promptly and properly applied in response to a dengue case. Insecticide applications are most effective when applied inside homes where most *Ae. aegypti* rest (Ref) and otherwise avoid contact with insecticides applied outdoors (Ref).

Though our study design was rigorous, our conclusions must be considered in the context of largely logistical limitations: (1) We did not sample all children and mosquitoes within the cluster area. (2) We were unable to characterize the serotype of all DENV infections among village enrollees given restrictions in the frequency of collecting blood from children. (3)

We did not collect data on human mobility/behavior that may have influenced the dynamics of transmission within the villages. (4) The possible contribution of adults to DENV transmission was not studied. (5) We did not study the seroprevalence profiles of cluster enrollees. Future studies should focus on positive clusters to more fully characterize the transmission dynamics, the impact of human behavior on transmission patterns, the appropriate spatial scale for disease surveillance/control, and identify more practical and cost-effective approaches to rapid dengue diagnosis.

Our cluster methodology provided additional epidemiologic insights. Of note, 14 of the 27 cases of dengue among enrollees were clinically inapparent during this period when DENV-4 was the primary serotype circulating. Most (five of six) primary DENV infections detected in our study were clinically inapparent, similar to observations during a predominantly DENV-2 transmission year in Bangkok [38]. The nearly 1:1 ratio of inapparent to symptomatic secondary DENV infections in our study is also consistent with previous results from KPP [19]. DHF occurred in one (8%) of 12 symptomatic infections and one (4%) of 27 DENV infections confirming that severe dengue represents only a small fraction of the total DENV burden. Future cluster studies can complement these clinical and virologic data by examining correlates of protection that limit transmission, early immunologic events via postinoculation pre-illness specimens and their association with disease severity and sequence variation among viruses through time and space as they circulate between human and mosquito hosts.

The prospective cluster methodology utilized here and by others (Ref) has the potential for broad application. It can be used for multidisciplinary transmission studies of other vector-borne viral diseases as well as spatially and temporally clustered infectious diseases.

Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer

This study demonstrated that HRMRI is highly accurate in prediction of transmural tumor invasion depth, mesorectal fascia invasion, adjacent organ invasion, and lateral pelvic lymph node metastasis which are essential for preoperative decision making in rectal cancer treatment. Contrarily, HRMRI is moderately accurate in prediction of mesorectal lymph node metastasis when using size criteria.

In general, patients with T1 tumors invading the submucosa are candidates for local excision, which is minimally invasive and promises excellent maintenance of anorectal and genitourinary functions.⁴ Patients with T2 tumors invading the muscularis propria, or T3 tumors invading the mesorectum but not invading the mesorectal fascia can be treated by TME, which maintains good genitourinary functions and fair anorectal function if the anal sphincter can be preserved.¹⁶ Patients with T3 tumors invading the mesorectal fascia or T4 tumors invading the adjacent organs require resection of adjacent tissues or organs.¹⁷ In addition, because surgical margins are directly related to prognosis,^{18,19} patients with threatened margins are candidates for neoadjuvant chemoradiotherapy.²⁴ Accurate prediction of local tumor invasion depth is thus essential for selecting an appropriate treatment for individual patients.

Although numbers of studies assessing the performance of HRMRI differentiating each T stages have been limited, agreements between HRMRI and histologic T-stages were reported to be constantly good and the weighted κ values ranged from 0.67 to 0.77.^{12,25} We also confirmed high accuracy in T-staging with weighted κ value of 0.84. Variations in these values are mainly attributable to number of stages differentiated in each study. The more stages the study adopts, the lower the κ value becomes. Although experience of a reader can also influence the results,¹² intraobserver agreement in experienced readers is good.^{12,14} In diagnosis of mesorectal fascia and adjacent organ invasion, HRMRI steadily

showed excellent overall accuracy ranging 88–100%^{12,24,25} and 100%,^{12,25} respectively, and so were our results. Such high accuracy has not been achieved by digital rectal examination,^{10,24} EUS,¹⁰ conventional CT¹⁰ and MRI,¹⁰ and multi-detector row CT.²⁶

To our knowledge, there has been no study on preoperative evaluation of the lateral pelvic lymph nodes including the internal iliac and obturator nodes by HRMRI so far. We found that HRMRI is highly accurate in diagnosis of lateral pelvic node metastasis and our sensitivity and specificity per patient were both up to 87%. As recommended in the Guidelines 2000 for Colon and Rectal Cancer Surgery,¹⁷ in the context of clinically suspected lateral lymph node disease, the dissection should attempt to remove these nodes, as is technically feasible.¹⁷ The incidence of lateral node involvement was 14% in this study and was 17% in the patients with T2 or more rectal cancer located below the peritoneal reflection.²⁷ The 5-year survival rates of the patients who had lateral node metastasis and had undergone lateral node dissection are 42–46%.^{27,28} On the other hand, lateral dissection is known to potentially damage the pelvic autonomic nerves which are essential for genitourinary function.²⁹ Therefore, decision whether to perform extended lateral pelvic lymph node dissection should be based on HRMRI findings. We mostly used a size criterion which was reported only moderately accurate for the prediction of mesorectal lymph node metastasis.^{30,31} However, as Fig. 5B shows, overlapped area of histograms of negative and positive lateral nodes is substantially small. And most patients without such metastasis had only tiny nodes or no detectable nodes. Therefore, the size criterion works well in this situation. Nevertheless, further improvement of the accuracy may be achieved by using ultrasmall superparamagnetic iron oxide (USPIO)^{32,33} as discussed below.

As to prediction of mesorectal lymph node metastasis per patient, **weighted κ value** of this study was moderate (0.48) and was comparable to 0.52–0.54 of the previous studies using size criteria (**weighted κ values were** calculated from original data).^{31,32} As Fig. 5A shows, overlapped area of histograms of negative and positive mesorectal nodes is not so small that the size criteria do not work so well for mesorectal lymph nodes as for lateral pelvic lymph nodes. To improve the accuracy, Brown et al.³⁰ proposed usage of the border contour and

signal intensity characteristics of lymph nodes and improved the weighted κ value from 0.52 with size criteria to 0.72 with border and intensity criteria (**weighted κ values were** calculated from original data). Kim et al.³¹ reported that in addition to size, new criteria such as a spiculated or indistinct border and a mottled heterogeneous appearance could be useful to predict lymph node involvement. More over, Koh et al.³² used USPIO enhanced HRMRI and reported association of lymph node enhancement patterns and metastasis. Recently, Lahaye et al.³³ examined 28 rectal cancer patients with USPIO-enhanced HRMRI and compared accuracy of 7 criteria for predicting mesorectal node involvement which included border irregularity, short- and long-axis diameter, and estimated percentage of white region.³³ And they found that estimated percentage of white region is reproducible, the most accurate, and the most practical.³³ Therefore, at present, accuracy of such criteria based on USPIO-enhanced HRMRI seems to be the best, and the accuracy should be prospectively tested in a larger cohort.

There are limitations to the present study. First, although data were prospectively accumulated, the study design is retrospective and this may cause biases. And single institutional experience may limit the wider applicability of our findings. Thus, present observations should be validated in a prospective multi-institutional study. Second, we could not use USPIO which is recently shown to improve accuracy of lymph node metastasis.^{32,33} In stead, we mainly used size criteria in combination with lymph node morphology and signal intensity and achieved high accuracy in prediction of lateral pelvic node metastasis but only moderate accuracy in prediction of mesorectal lymph node metastasis.^{30,31} Therefore, usage of USPIO is recommended in future trial.

In conclusion, the present observations indicate that HRMRI was moderately accurate in prediction of mesorectal lymph node metastasis but HRMRI was highly accurate in prediction of transmural invasion depth and mesorectal fascia and lateral pelvic node involvement. Therefore, HRMRI is useful for preoperative decision making in rectal cancer treatment.

Survey of the general public's attitudes toward advance directives in Japan: How to respect patients' preferences

Discussion

This study revealed that many middle-aged and senior people in Tokyo indicate an interest in undertaking advance directives. Nearly three-quarters (73.7%) of respondents in this study said that they would like to verbally express their treatment preferences in advance. This result is reflected in other research conducted in Japan which found that 80.5% of a general public sample strongly/moderately agreed with advance directives [12]. However the fact that only 20.3% of the people in our study had already undertaken advance directives indicates that despite a interest, barriers exist to carrying this out (Table 2). While there is strong recognition of the benefits of undertaking advance directives with over 60% of respondents agreed that it is preferable to express their wishes regarding the appointment of a proxy for care decisions, appointment of a legal administrator of property, stating preferences regarding one's property and funeral arrangements, less than 10% of them had already done so (Table 2). The existence of a number of barriers to undertaking advance directives has been identified in the literature. Research indicates that Japanese people have difficulty in actually expressing their preferences regarding advance directives even in the case that they are willing do so[32] Furthermore, dementia has been identified as contributing to difficulties in encouraging advance directives policies. Our former study showed that of the nursing homes in Japan that confirm their residents' preferences regarding advance directives, for the most part, this is only undertaken some time after patients have been admitted [31]. However, this may be inappropriately late given that more than a majority of residents have difficulties in daily life due to dementia. While it is clear that it is highly desirable for patients to undertake advance directives before dementia has reached advanced stages, in many cases, treatment preference made might not be respected because of patients' difficulties in expressing preferences and nursing home attitudes that do not validate advance directives in a positive way. In order to ensure that the treatment

preferences of the general public in Japan are recognized and met, some support for individuals as well as nursing homes and medical professionals is necessary.

About 60% of respondents in this study preferred to indicate treatment preferences in broad rather than concrete terms. Over 80% would like to decide treatment preferences in consultation with others (22.2% with their proxy, 11.0% with the doctor, and 47.8% with both their proxy and the doctor) and over 75% of respondents would like the opportunity to discuss their treatment preferences with their proxy more than once (51.2% when clinical conditions require, 25.4% regularly). Respondents' responses reflected a range of preferences regarding how advance directives are undertaken, thus it is important to recognize that any processes put into place should allow flexibility in order to best respect patients' wishes and autonomy. In the case of shared treatment decision-making, further investigation is required to examine what processes would be appropriate in order to respond to patients and their surrogate decision makers' desires.

Even in the case of advance directives that does not specify detail, patient wishes do need to distinguish between preferences that arise in the cases of different kinds of complications that occur toward the end of life including irreversible coma, dementia and temporary illness. Respondents' preferences varied amongst the scenarios for the four active treatments and all the life-sustaining treatments. Moreover results of factor analysis for three of the scenarios are slightly different with patient preferences ranged from high rates of desire to receive treatments in the event of temporary illness to high rates of treatment rejection in the case of irreversible coma. Similar results have also been reported elsewhere [33,34]. In research conducted in Japan on advance directives making in the event of terminal illness, Asai [19] suggested that Japanese terminally patients, despite having competency to do so, might not actually be able to make their advance directives concrete enough to guide physician's decisions. Given these findings, it might be need to consider distinguishing diagnoses for which a Japanese advance directive format applies or does not apply.

This research found that the burden of treatment and the likelihood of outcome all

influenced treatment preferences, consistent with results found in another study [25]. The results of the factor analysis on preference suggest that patient' preferences toward LSTs and burden of treatments should always be confirmed when asking about treatment preferences in end-of-life situation. However LSTs accounted for the nearly half of the total variance in the analyses conducted on each scenario. As four types of high burden ATs were Factor 2 in both the dementia and temporary illness scenarios and 4 types of low burden ATs were Factor 3 in the irreversible coma scenario, the second biggest factor affecting preferences might be the perceived level of burden of ATs. If patients would like to indicate treatment preferences in a broad sense rather than concrete terms, it might be possible to do so by putting all LSTs and high burden treatments in one category, without specifying treatment. Further studies will be required to confirm whether this simplification is appropriate or not.

This research's results suggest that type of diagnosis given to the general public members in this sample and their characteristics have little effect when they have only severe treatment outcome. Three of the scenario groups showed no significant differences in preferences to four types of active treatments, of which at least two had negative attributes of burden, chances of success and life expectancy. On the other hand respondents' characteristics did not affect treatment preferences in the irreversible coma scenario, while many characteristics significantly affected preferences in the other two scenarios. Many respondents refused high burden, poor likelihood treatments even in temporary illness scenario which is relatively healthy state. As temporary illness is defined "decisional incapacity state cause by such as mental disorders, and people would soon recover capacity", respondents might consider their choice only for incapacity period.

As this study is a cross sectional survey in Japan, these results may not be simply applicable to other country. Though the desire for group decision making might be different in Japan in comparison to Western countries, a former study suggests that Japanese patients' preference for disclosure, willingness to forgo care, and views regarding advance directives are shifting toward those found in the West [35]. As respondents' preferences regarding

life-sustaining treatment in this study (23%–36% wanting LSTs in the case of dementia; 21%–33% wanting LSTs in the case of Coma) are similar to those found in the United States (23% to 42% wanting LSTs in the case of dementia; about 14–29% wanting LSTs in the case of Irreversible coma [17, 23], our previous study shows a similar tendency between the two countries regarding patients' preferences and cancer disclosure [36]. Despite differences between Japanese and western and US medical institutional policies and doctors' attitudes regarding advance directives [37], it is suggested that there is little difference in patients' side preferences regarding treatment preferences.

We would like to make a couple of comments on the representative-ness of this survey's sample. The response rate for this study was generally good for a general population survey, though slightly lower than that of a similar Japanese study which found that 80.5% of respondents strongly/moderately agreed with advance directives [12]. We therefore believe that the response rate did not significantly affect the overall results obtained in our study. However, this study's sample was limited to residents who reside in Tokyo aged between 40 and 65. As Tokyo is the most condensed and diverse metropolitan area in Japan, further research is needed in order to collect and compare our results with data collected in rural areas and smaller towns and cities. It is also required to add younger (under the age of 40) and older people (over the age of 65) in further research to consider generalization of these findings.

In order to respect Japanese patients' preferences, it might be important to implement flexible processes and practices that are able to accommodate patients' preferences as well as nursing homes and medical professionals' needs regarding advance directives and surrogate decision making. Specific to the Japanese context, the results of this survey indicate that advance directives might need to differentiate processes according to diagnoses including LSTs and high burden ATs treatment items.

Cardiovascular risk and prevalence of metabolic syndrome by differing criteria

Discussion

To our knowledge, this is one of the early studies to compare the prevalence of MetS using definitions of NCEP, IDF and the revised NCEP and to investigate the association between MetS and target organ damage in a large rural population with hypertension in China. Because the two major aetiological factors (insulin resistance and central obesity) underlying the MetS are influenced by gender, and the diagnostic criteria of MetS are different between men and women, we conducted the assessments by gender separately (Ref).

Our results showed that the prevalence of MetS in hypertensive patients was high: nearly 1/3 of male patients and 1/2 of female patients could be diagnosed with MetS by the revised NCEP or IDF definitions. Previous studies have shown varied prevalence of MetS as different definitions were used or the subjects had genetic disposition and lifestyle. For example, the National Health and Nutrition Examination Survey found that the age adjusted prevalence of MetS is 34.4% among men and 34.5% among women, but 62.9% in hypertensive patients by NCEP definition (Ref). A survey conducted in China found that the age standardized prevalence of NCEP defined MetS is much lower in Chinese (9.8% in men and 17.8% in women respectively) (Ref). Using WHO definition, more than half of hypertensive patients have been found to have MetS in Shanghai urban areas.¹⁵ In our study, the prevalence of MetS was higher in hypertensive women than in hypertensive men, which is consistent with the pattern of MetS prevalence in the general population in China(Ref). Our study indicated that both IDF and revised NCEP definitions were equally sensitive in identifying patients with MetS and this was consistent with the results in the study of USA population (Ref).

Most studies have indicated that MetS is associated with increased risk of CHD and stroke. Ninomiya et al (Ref) found that MetS (NCEP) is associated with history of myocardial infarction and stroke. A recent metaanalysis, using 37 eligible studies including 43 samples (1971 to 1997) with 172 537 individuals, showed that people with MetS are at increased risk of cardiovascular events and death (Ref), however, the results are still controversial. Aging has been known to increase collagen crosslinking and arteriosclerosis independently of the components of MetS (Ref), so age difference of the participants may contribute partially to the inconsistency.

Recently, researchers have paid close attention to cardiovascular diseases of females. The Women's Ischemia Syndrome Evaluation (WISE) study indicates that in women with suspected myocardial ischaemia, the presence of the MetS is a strong prognostic predictor for future cardiovascular events.²⁵ In ischaemic stroke population, half of acute ischaemic stroke patients have MetS and MetS is more frequent in women than in men.²² This could be explained by the stronger correlations between components of MetS in women than in men.^{26,27} Our study also indicated that the prevalence of MetS were 1.6 and 3.2 times more in women with CHD or stroke than in men with CHD or stroke. After adjusting for age, smoke and alcohol use, the MetS remained independently associated with CHD and stroke in the female hypertensive sample.

In a prospective study of 750 subjects who underwent coronary angiography, the NCEP definition of the MetS yields a significantly higher risk of vascular events than does IDF definition.¹³ A recent study has shown that the revised NCEP definition in males and the IDF definition in females is the strongest predictors of carotid atherosclerosis.¹⁴ The results from three recent studies in China (two in samples aged from 58 to 85 years,^{28,29} one in patients diagnosed with type 2 diabetes³⁰) showed that IDF defined MetS is more strongly associated with cardiovascular events than NCEP defined, but the revised NCEP definition was not evaluated. Our study confirmed that the IDF defined MetS was more strongly associated with CHD than NCEP or the revised NCEP defined MetS in both men and women. However, IDF definition was weakly or not associated with stroke in the patients

with hypertension. It is well known that hypertension is a more dangerous risk factor to stroke than to CHD. Our enrolled individuals are hypertensive patients, so the OR values were equal when adjusted for hypertension, which might result in the weak association between IDF defined MetS and stroke.

Our study is subjected to certain limitations. Many male inhabitants had left their towns to work in urban areas during the study period. Consequently, our study included more women than men. If the men who left are healthier than the men who stayed at home, it is possible to overestimate the prevalence of MetS in this population, but the prevalence of MetS in hypertensive patients may not be biased.

In summary, the prevalence of the MetS is high in the hypertensive in rural areas of China. The IDF and revised NCEP definitions could identify a higher proportion of individuals than NCEP definition and their agreement is very high. The IDF defined MetS is more strongly associated with CHD than the NCEP or revised NCEP defined MetS, but weakly or not associated with stroke in the patients with hypertension.

Introduction

**What is the problem,
what is the model,
what are the techniques**

Why? What? How?

First paragraph: Statement of the field

What known

What not known

2nd paragraph: Models

Advantages/Disadvantages

Last paragraph: Specific aims

Approach adopted to clarify

Precautions

Additional aims

Sample 1

Risk of Stroke in Relation to Level of Blood Pressure and Other Risk Factors in Treated Hypertensive Patients

Introduction

Mortality due to stroke has been declining in Japan, as in most countries, but stroke is still the second leading cause of death in Japan (Ref). Hypertension is the most powerful risk factor of stroke, and higher levels of systolic and diastolic blood pressure (BP) have been associated with an increased incidence of ischemic and hemorrhagic stroke in people of all ages and both sexes (Ref). Many intervention studies have demonstrated that antihypertensive therapy effectively reduces morbidity and mortality of stroke in hypertensive subjects, including elderly patients with isolated systolic hypertension (Ref). Therefore, there is no doubt that control of hypertension is particularly important for the prevention of stroke.

However, there is persistent excess cardiovascular morbidity in treated hypertensive patients ((Ref). The level of BP before the onset of stroke is less well characterized, and the risk of stroke in treated patients has not been clarified well. A number of treated patients still have high BP and often have other cardiovascular risk factors and complications (Ref). The incomplete control of hypertension may be related to the risk of stroke (Ref). On the other hand, an excessive decrease in BP may increase cardiovascular complications. We observed previously that low diastolic BP is associated with increased recurrence of stroke or myocardial infarction (Ref). It has also been suggested that the level of optimal BP may be age dependent.

A large number of hypertensive patients have been treated at our outpatient clinic, and >90% of those patients who suffered from stroke were admitted to the Stroke Care Unit of our

hospital. In the present case-control study, we analyzed the relation between the level of BP and the risk of first stroke using multiple BP readings over 1 year before the onset of stroke, with particular attention to BP at 1 month before onset. We also analyzed other cardiovascular risk factors and complications in relation to the risk of stroke.

Sample 2

Spatial and Temporal Clustering of Dengue Virus Transmission in Thai Villages

Dengue is the leading cause of human arboviral disease worldwide. Dengue viruses (DENV) of the family Flaviviridae and genus Flavivirus, co-circulate as four antigenically related serotypes (DENV-1, -2, -3, and -4), each in varying annual frequencies in Thailand (Ref) and other tropical countries. The container-breeding mosquito *Aedes aegypti* (L.) serves as the primary vector responsible for DENV transmission within human populations. Females feed preferentially and frequently on human blood and consequently live in and around human dwellings (Ref). Transmission of DENV to humans results in either inapparent infection, undifferentiated febrile illness, dengue fever (DF), or life-threatening dengue hemorrhagic fever (DHF). Except for a few notable exceptions, vector control (larvicide treatments, insecticide sprays, and source reduction) has been ineffectively implemented, and no vaccine or clinical cure is yet available for use. Consequently, DENV remain a major cause of morbidity in the tropics and threaten to further expand geographically.

DENV transmission and disease are determined by a combination of factors (Ref) involving the human host (Ref), virus (Ref), mosquito vector (Ref), and environment (Ref). Although past studies have revealed general temporal and spatial patterns in the distribution and abundance of *Ae. aegypti* and human DENV infections (Ref), greater resolution of transmission dynamics across finer geographic and temporal scales is needed to refine current dengue surveillance and control strategies.

In an earlier prospective cohort study of schoolchildren in Thailand, Endy and others (Ref) reported a nonuniform distribution of DENV illness and viral serotypes. To test the hypothesis that DENV transmission is spatially and temporally focal, we extended the school-based study design to include cluster investigations (Ref) in villages associated with schools. By sampling children and mosquitoes within the neighborhood of children absent from school with fever and dengue viremia, we hypothesized that we would be able to detect, in the same general area and time, other human and mosquito infections and more precisely identify determinants of transmission risk. We used school-based dengue cases to trigger village surveillance of children and mosquitoes within spatial and temporal clusters. We sought a rigorous study of cluster areas over a 15-d period to more accurately define the burden of DENV within a prescribed area (both inapparent and symptomatic infections) and its relationship to mosquito density and infectivity. On the basis of our data, we aimed to consider implications on improving disease prevention strategies.

Sample 3

Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer

The principal problems with rectal cancer surgery are local recurrence and impairment of genitourinary and anorectal functions after surgery. The pelvic autonomic nerves which are essential for genitourinary function are located just outside and adjacent to the mesorectal fascia. Genitourinary function can be unnecessarily damaged by inaccurate surgery or excessive resection, and so can anorectal function, while insufficient resection leads to local recurrence. Therefore, to achieve better prognosis and maintain better quality of life, the extent of surgical resection should accurately reflect the disease status.

This is also true for adjuvant therapy. Since several randomized controlled studies showed benefit of neoadjuvant radiotherapy in reducing local recurrence² and prolonging survival,³ radiotherapy became a standard practice for T3–4 or node positive tumors. However, surgery alone can provide local control in almost all T1 or T2 tumors⁴ and in many T3–4 or node positive tumors.⁵ In addition, radiotherapy is well known to have the potential to cause damage to anorectal^{6,7} and sexual^{8,9} functions. Therefore, the adjuvant therapy adopted should also accurately reflect the disease status.

The extent of tumor spread is conventionally evaluated by digital examination, endorectal ultrasonography (EUS), computed tomography (CT), and magnetic resonance imaging (MRI). In evaluation of local invasion, EUS was reported to be superior to CT and MRI.¹⁰ However, EUS can not visualize the mesorectal fascia and lateral pelvic lymph nodes including internal iliac and obturator nodes, and is not applicable for stenosing tumors so that further improvements are still necessary for optimum tailoring of treatment for the individual patient.

Recent advances in medical imaging demonstrated that high-resolution MRI (HRMRI) is accurate in preoperative evaluation of local invasion^{11,12} and mesorectal lymph node metastasis¹³ of rectal cancer. Our previous study also showed that HRMRI is accurate and reliable for preoperative evaluation of pelvic anatomy and depth of transmural invasion.¹⁴ The purpose of the present study was to extend our experience and evaluate accuracy of HRMRI in preoperative evaluation of transmural tumor invasion depth, mesorectal fascia involvement, mesorectal lymph node metastasis, and lateral pelvic lymph node metastasis which are essential for clinical decision making.

Sample 4

Survey of the general public's attitudes toward advance directives in Japan: How to respect patients' preferences

Introduction

In recent times, paternalistic decision making practices and policies regarding life prolonging treatments have widely been replaced by an emphasis on patient participation, respect for autonomy, and quality of life (Ref). Research indicates that honoring the treatment preferences of terminally ill patients is critical for the provision of high quality care at the end of life (Ref). Advance care planning including living wills and health care proxies have become established to facilitate ways for patients to specify the kind of medical treatment they desire in the case of incapacitation. The designation and presence of a health care proxy is significantly associated with higher patient satisfaction with comfort care plans (Ref). Patients' preferences are most often elicited through advance directives, and discussions regarding advance directives could provide a framework for all treatment related decision-making between medical professionals and patients in addition to protecting patients in the event of decisional incapacity (Ref).

In the United States, all 50 states and the District of Columbia have passed legislation on advance directives (Ref). In the United Kingdom, although the British Medical Association cautiously approved the introduction of advance directives in a statement in May 1992 (Ref), there is still no legislation which deals with patient autonomy in the case of terminal illness. This is similar to the situation in Japan where, although the Japan Medical Association has officially declared that a patient's advance request for death with dignity should be respected (Ref), advance directives have no legal standing.

While the general public in Japan have become increasingly interested in the expression and enhancement of their individual autonomy in medical decisions made at the end of life (Ref), one study has suggested there are several possible barriers in the appropriate use of advance directives (Ref). In dealing with terminal patients, moreover, another study indicated that only half of Japanese doctors gave priority to their patients' wishes for medical care regardless of the patient's competency(Ref). In the light of this, there is a need to investigate patient's preferences regarding treatment at the end of life in order to re-evaluate advance directives policy and practice.

More than 103,000 people have joined the Japan Society for Dying with Dignity and have formulated a living will [18]. Though the advance directives format used by the Society gives no choice in terms of declaring wishes regarding treatment options, several researchers in the advanced directives field have pointed out that the desirability of making an advance directive depends on its outcome (e.g. life expectancy, chance of success) [19-21]. As both qualitative[22] and quantitative data [23,24] support the importance of outcomes in patients' treatment preferences, recent research indicates that advance directives should take into account patients' attitudes toward the burden of treatment, the possible outcomes, and their likelihood [25]. In order to examine the suitability of processes for advance directives from the patient's perspective in Japan, we conducted a population-based survey to clarify the general public's preferences to treatment with differing burden, outcomes and likelihood assuming that this group might best represent patients' attitudes.

Sample 5

Cardiovascular risk and prevalence of metabolic syndrome by differing criteria

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including centrally distributed obesity, decreased high density lipoprotein cholesterol (HDL), elevated triglycerides, hypertension and hyperglycaemia. Due to changes in the human environment, behaviour, lifestyle and diagnostic criteria of MetS, substantial numbers of people with MetS have been diagnosed over the past two decades. As an important risk factor for heart disease, stroke and diabetes (Ref), the MetS has become a serious public health problem.

Since its initial description by Reaven in 1988 (Ref), several definitions for MetS have emerged in an attempt to provide a useful tool for clinicians and researchers. The first global definition of MetS was by the World Health Organization (WHO) in 1998 (Ref), however, the requirement of using euglycaemic clamp to measure insulin sensitivity made the WHO definition virtually impossible to be used in either clinical practice or epidemiological studies. Two years later, the National Cholesterol Education Program (NCEP) of the USA introduced the NCEP definition which assumes that MetS is a clinical utility by treating all its components as equally important and does not include a specific measure of insulin (Ref). The NCEP definition became popular because of its simplicity and feasibility in that its components could be easily and routinely determined in most clinical and research settings. The NCEP definition of central obesity may not be necessarily appropriate for Asians because of a greater tendency to develop cardiovascular diseases at lower waist circumferences than Western populations (Ref).

In 2005, the International Diabetes Federation (IDF) presented an improved definition applicable to clinical practice worldwide (Ref). The definition recognizes central obesity as an important criterion of MetS. IDF has recommended that the cut off points for waist circumference should be specific to an ethnic group. Meanwhile, AHA/NHLBI revised the NCEP definition to waist circumference ≤ 90 cm for Asian men and ≤ 80 cm for Asian women as IDF definition did (Ref).

It has been shown in a study conducted in the general population of USA, that revised NCEP and the IDF are consistent (Ref) but not validated among a hypertensive population. A purpose in diagnosis of MetS is to identify people at high risk of cardiovascular diseases. Because the life style and physical activity of countryside people are quite different from urban populations, we wondered which definition of MetS is associated with the cardiovascular risk more effectively (Ref), especially in the hypertensive rural population (Ref).

This study compared the prevalence of MetS according to NCEP, the revised NCEP and IDF definitions and investigated the association between MetS and coronary heart disease (CHD) and stroke in patients with hypertension in rural areas of China.