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ORIGINAL ARTICLE

Malignant neoplasms of the sinonasal tract: report of 71 patients and literature review and analysis

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Abstract
Background The present study aimed to report the characteristics, prognostic factors, and treatment outcomes of 71 cases of malignant neoplasms of the sinonasal tract and literature review and analysis of major report series.
Methods Seventy-one consecutive patients diagnosed with primary malignant neoplasm of the sinonasal tract that were treated and followed up at a university hospital between May 2000 and March 2008 were selected for the present study. Thirty-four patients were treated with surgery followed by a combination of chemotherapy and radiotherapy, 15 with surgery alone, 14 with combined radiotherapy and chemotherapy, six with radiotherapy alone, and two with surgery followed by radiotherapy. To find out the major series of related studies over the last 20 years, a literature review of PubMed was performed. In all, we found 42 major series including 8,164 patients with malignant neoplasms of the sinonasal tract.
Results There were 35 women and 36 men ranging in age from 5 to 80 years, with a median age of 55 years at diagnosis. The primary sites included were paranasal sinuses in 51 and nasal cavity in 20. There were one case of stage I, 20 of stage II, 27 of stage III, and 23 of stage IV. Epithelial tumors constituted 65% of all neoplasms. After a median follow-up of 39 months for surviving patients, 33 patients are alive and without disease, eight are alive with disease, and 30 patients died due to disease. Local recurrence was the most frequent treatment failure. The 5-year disease-free, local control, and overall survival rates were 42.1%, 59.5%, and 54.5%, respectively. On univariate analysis, cervical lymph nodes involvement, primary tumor size, histologic type, response to therapy, and stage of disease were independent prognostic factors for overall survival. In the literature review and by analyzing the data collection from 42 major reported series, the median age was 57 years and male/female ratio was 1.8. Epithelial tumors consisted of 69% of all malignant neoplasms of sinonasal tract and stages III and IV disease constituted 74.7% of all stages. Local recurrence was the dominant treatment failure in nearly all series. Five-year local control and overall survival rates were 56% and 45.5%, respectively.
Conclusions In this review and by analyzing the large data collection of recent major reported series, we found that malignant neoplasms of the sinonasal tract tend to present at locally advanced stage, with a high frequency of local failure and a moderate to poor outcome. More effective local treatment for improving the local control and overall survival is needed.

Keywords Malignant neoplasms · Head and neck · Sinonasal tract · Nasal cavity · Paranasal sinuses · Surgery · Radiotherapy · Chemotherapy

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Introduction

Malignant neoplasms of the sinonasal tract (paranasal sinuses and nasal cavity) are relatively rare, representing

less than 1% of all malignant tumors [1, 2]. These neoplasms are diverse pathologies that tend to present at locally advanced stage, with a high frequency of local failure and a moderate to poor outcome. Epithelial tumors constitute the majority of these malignancies [3, 4]. Squamous cell carcinoma, minor salivary gland tumors, and undifferentiated carcinoma are the most frequent malignant epithelial neoplasms in this region. Esthesioneuroblastoma and malignant melanoma are the most common nonepithelial pathologies. Maxillary sinus and nasal cavity are the most frequent primary sites, followed by ethmoid, sphenoid, and frontal sinuses [5, 6]. The proximity to critical structures, in particular orbital fossa, brain, and cranial nerve, makes a therapeutic challenge for eradicating these neoplasms with a safe margin [7, 8]. There is no consensus regarding the optimal treatment in patients with malignant neoplasm of sinonasal tract because of the rarity and diverse biological behavior of the disease. Surgery and/or radiotherapy are the cornerstones of locoregional treatment for these malignancies [9–12]. According to the histology and stage of disease, adjuvant chemotherapy may be suggested [8, 11, 13, 14]. The present study aimed to report the characteristics, prognostic factors, and treatment outcomes of 71 cases of malignant neoplasms of the sinonasal tract and a literature review. In addition, this study represents a quantitative summary and analysis of pooled data collection of major related studies including more than 8,000 cases.

Materials and methods

Seventy-one consecutive patients diagnosed with primary malignant neoplasms of the sinonasal tract that were treated and followed up at a university hospital between May 2000 and March 2008 were selected for the present study. The median age of the patients was 55 years (range 5 to 80 years). There were 35 women and 36 men with a median follow-up of 39 months (range 9 to 111 months) for living patients.

Staging

The sixth edition of the American Joint Committee on Cancer staging classification was used for the most histologic types [15]. Lymphomas were staged according to the Ann Arbor staging system of Hodgkin's disease. For esthesioneuroblastoma, primary tumors confined to the nasal cavity were considered as stage I, those involving the nasal cavity and paranasal sinuses as stage II, and tumors extending beyond the nasal cavity and paranasal sinuses or any primary tumors with positive cervical lymph nodes were defined as stage III. The staging of malignant melanomas was determined according to the following basic staging system: The lesions confined to the primary site were defined as stage I, regional cervical lymph node involvement as stage II, and distant metastasis as stage III.

Treatment

Thirty-four patients were treated with surgery followed by a combination of chemotherapy and radiotherapy, 15 with surgery alone, 14 with combined radiotherapy and chemotherapy, six with radiotherapy alone, and two with surgery followed by radiotherapy.

Chemotherapy

The chemotherapy regimen mainly consisted of cisplatin 80 mg/m^2 on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1 to 3 for epithelial tumors. Approximately two thirds of the patients received a median two (range one to six) cycles of chemotherapy. Doxorubicin-based chemotherapy was used for patients with sarcoma and lymphoma histologic types. Single-agent dacarbazine was considered as systemic treatment for patients with malignant melanoma.

Radiotherapy

Fifty-eight patients received adjuvant or definitive external beam radiotherapy using cobalt-60 units and/or 9 MV X-ray photons or electrons from a linear accelerator. A median dose of 60 Gy (range 30 to 75 Gy) was delivered via a daily fraction of 2 Gy, with five fractions per week. A three-field technique (one anterior and two laterals wedged) or a wedge pair technique was mainly used.

Definition of response and survival

A complete response was defined as complete resolution of all clinically evident disease with normalization of laboratory values and imaging studies. A partial response was defined as at least 50% reduction in the mass and not meeting the criteria for complete response, and finally, a less than 50% reduction was considered no clinical response.

Statistical analysis

Disease-free survival was calculated from the date of registration to the date of disease relapse at any site. Overall survival was calculated from the date of registration to the date of death due to any cause. Univariate analysis for disease-free survival and overall survival rates

was performed using the Kaplan–Meier method, and prognostic factors were compared using the log-rank test. Multiple-covariate analysis was performed using the stepwise Cox's proportional hazards regression model. The hazard ratio for death, with the 95% confidence interval, was calculated for the treatment groups. The stratified log-rank test was used to compare treatment results in each disease group. *P* values less than 0.05 were considered statistically significant.

Results

Age and sex distribution

There were 35 women and 36 men ranging in age from 5 to 80 years, with a median age of 55 years at diagnosis. The peak incidence was during the sixth and seventh decades of life in both sexes. Forty patients were more than 50 years old at presentation and 31 patients were less than or equal to 50 years old.

Histologic distribution

There were 19 squamous cell carcinoma, 18 adenoid cystic carcinoma, six undifferentiated carcinoma, three adenocarcinoma, seven lymphoma, six esthesioneuroblastoma, six malignant melanoma, three sarcoma, and three miscellaneous tumors. In all, epithelial tumors constituted 65% of all neoplasms (Table 1).

Distribution of the primary site and stage of the disease

The primary sites included were maxillary sinus in 29, ethmoid sinus in 18, sphenoid sinus in three, frontal sinus in one, and nasal cavity in 20. One patient (1.5%) had stage I disease, 20 (28%) had stage II disease, 27 (38%) had stage III disease, and 23 (32.5%) had stage IV disease, as detailed in Table 2.

Response to therapy and survival rates

A complete response was achieved in 42 patients (59.2%) during or after initial treatment. Twenty-five patients (35.2%) had partial response and four patients (5.6%) had no response to initial treatment. Therefore, overall response rate was 94.4%. All nonresponding or partial responding patients to the initial treatment were treated with salvage alternative treatment. After a median follow-up of 39 months for surviving patients, 33 patients were alive and without disease, eight were alive with disease, and 30 had died due to disease. Thirty-eight patients (53.5%) developed local, regional, or distant failure. Recurrences consisted of 11 patients (29%) with local recurrences; seven patients (18%) with local and regional recurrences; one patient (3%) with local and distant metastases; four patients (11%) with local, regional, and distant metastasis; six

Table 1 Distribution of histologic types and primary sites

Histologic types	No. of patients	M/F ratio	Mean age	Primary sites (*n*)		5-year rates (%)		
				Nasal cavity	PNS	OS	DFS	LC
Epithelial tumors	46	0.84	50.1	14	32	61.9	49.6	64.7
SCC	19	0.58	52.9	2	17	51.5	52.6	68.4
Adenocarcinoma	3	0.0	54.6	1	2	66.7	66.7	66.7
ACC	18	1.2	47.0	6	12	82.4	51.6	75.0
Undifferentiated carcinoma	6	2	48.0	5	1	33.3	33.3	25.0
Non-epithelial tumors	25	1.5	52.0	6	19	42.6	30.2	51.2
Esthesioneuroblastoma	6	0.5	52.8	3	3	20.0	16.7	33.3
Lymphomas	7	0.75	53.0	1	6	57.1	57.1	71.4
Sarcomas	3	–[a]	12.3	0	3	33.3	33.3	50.0
Malignant melanoma	6	–[a]	70.5	2	4	25.0	16.7	55.6
Miscellaneous	3	–[a]	50.6	0	3	100	50.0	50.0
Total	71	1.02	51.03	20	51	54.5	42.1	59.5

Miscellaneous tumors included plasmacytoma, malignant myoepithelioma, and transitional cell carcinoma

SCC squamous cell carcinoma, *ACC* adenoid cystic carcinoma, *M/F ratio* male/female ratio, *PNS* paranasal sinuses, *OS* overall survival, *DFS* disease-free survival, *LC* local control

[a] All patients were male

Table 2 Distribution of disease stages and histologic types

Histologic types	Stage I (*N*)	Stage II (*N*)	Stage III (*N*)	Stage IV (*N*)	Total (*N*)
Epithelial tumors	0	14	14	18	46
Squamous cell carcinoma	0	6	5	8	19
Adenocarcinoma	0	0	2	1	3
Adenoid cystic carcinoma	0	8	7	3	18
Undifferentiated carcinoma	0	0	0	6	6
Nonepithelial tumors	1	6	13	5	25
Esthesioneuroblastoma	0	2	4	0	6
Lymphomas	0	1	3	3	7
Sarcomas	0	0	1	2	3
Malignant melanoma	1	2	3	–	6
Miscellaneous	0	1	2	0	3
Total	1	20	27	23	71

Miscellaneous tumors included plasmacytoma, malignant myoepithelioma, and transitional cell carcinoma

patients (16%) with regional recurrences alone; and nine patients (23%) with distant metastasis alone. The 5-year disease-free, local control, and overall survival rates were 42.1%, 59.5%, and 54.5%, respectively.

Prognostic factors

On univariate analysis, cervical lymph nodes status (P=0.035), primary tumor size (P=0.004), histological type (P=0.038), response to therapy (P<0.001), and stage of disease (P=0.049) were independent prognostic factors for overall survival. However, age (P=0.843), sex (P=0.829), primary site (P=0.318), and treatment schedule (P=0.035) were found not to be prognostic factors for overall survival. Univariate analysis for disease-free survival showed similar results (Table 3). On multivariate analysis, only response to therapy (hazard ratio 44.954; confidence interval 95%=6.024–335.480, P<0.001) and stage of disease (hazard ratio 1.821; confidence interval 95%=1.056–3.141, P=0.031) retained statistical significance.

Discussion

Malignant neoplasms of the sinonasal tract are relatively rare tumors encompassing an extensive diverse group of tumors with wide spectrum of biological activity and clinical behavior with many associated factors that make them different therapeutic and challenging approaches. As found in our study, these neoplasms usually occur in the sixth and seventh decades of life and rarely before the second decade. In the present study, the mean and median age of our patients were 55 and 51 years, respectively, which were consistent with the results of the literature review in which the average median age of 5,106 patients in the reported series was 57 years (Table 4) [4, 5, 9, 10, 12, 13, 16–34].

In almost all reported series in the literature review, men represent a higher proportion of malignant neoplasms of the sinonasal tract sufferers than women, with a mean male/female ratio of 1.8 (range from 1.2 to 5.3) in 30 studies including 6,518 patients [3–6, 9–13, 16–36]. However, in our series, there was no significant difference and the male/female ratio was nearly equal to 1.

Malignant neoplasms of the sinonasal tract usually present late and approximately three quarters of patients being diagnosed with stages III and IV disease [3]. In the literature review and according to the pooled data from 19 series including 3,705 patients, stages III and IV disease constituted 74.7% of all stages [3, 6, 9–11, 16–18, 20, 21, 23–25, 30, 32, 36–39]. In agreement with this mean value, in the present study, the majority of patients presented with locally advanced disease, and 70% had stage III or IV disease.

Epithelial tumors constitute the majority of sinonasal neoplasms. In the literature review and based on the pooled data from 22 series including 5,578 patients, carcinomas constituted more than two thirds of all malignant neoplasms of the sinonasal tract [3–6, 12, 13, 16–22, 24, 27–29, 32–34, 36, 40]. In our study, carcinomas constituted 65% of all pathologies, which is consistent with the results of the literature review. In the literature review and by analyzing data of 5,798 patients, maxillary sinus (39%), nasal cavity (33%), and ethmoid sinus (25%) were the most frequent primary sites. Furthermore, squamous cell carcinoma (35%) and minor salivary gland carcinomas (29%) were the most common histologic types. Table 5 shows the distribution of the primary sites and histologic types of 4,867 patients in the major reported series and 71 patients in the present study [4–6, 9–13, 16, 18–26, 28, 29, 33, 34, 40–45].

Table 3 Univariate analysis of prognostic factors for clinical outcome

Prognostic factors	No. of patients	5-year OS (%)	*P* value	5-year DFS (%)	*P* value
Age					
<55 years	38	50.2		44.3	
≥55 years	33	58.7	0.263	38.0	0.843
Sex					
Male	36	52.6		44.3	
Female	35	57.3	0.656	38.0	0.829
Primary site					
Paranasal sinuses	51	55.4		46.4	
Nasal cavity	20	40.9	0.948	31.6	0.318
Cervical lymph nodes					
Uninvolved	54	61.9		46.8	
Unilateral involvement	8	30.0		25.0	
Bilateral involvement	9	33.3	0.035	33.0	0.042
Tumor size					
<5 cm	39	69.1		56.8	
≥5 cm	32	36.8	0.004	23.3	0.001
Histology					
Squamous cell carcinoma	19	51.5		52.6	
Adenocarcinoma	3	66.7		66.7	
Adenoid cystic carcinoma	18	82.4		51.6	
Undifferentiated carcinoma	6	33.3		33.3	
Esthesioneuroblastoma	6	20.0		16.7	
Lymphomas	7	57.1		57.1	
Sarcomas	3	33.3		33.3	
Malignant melanoma	6	25.0		16.7	
Miscellaneous	3	100	0.038	50.0	0.023
Treatment					
RT ± ChT	20	57.9		46.4	
Surgery alone	15	45.7		45.7	
Surgery + RT ± ChT	36	57.5	0.772	36.4	0.961
Response to therapy					
No response	5	00.0		00.0	
Partial response	32	19.1		12.5	
Complete response	34	96.4	<0.001	78.2	<0.001
Stage of disease					
I	1	00.0		00.0	
II	22	73.4		61.5	
III	25	54.1		31.3	
IV	23	39.1	0.049	34.8	0.050

RT radiotherapy, *ChT* chemotherapy

The incidence of cervical lymph node involvement at presentation is low in malignant neoplasms of the sinonasal tract; however; elective neck management in locally advanced disease or with early primary disease and unfavorable histology such as undifferentiated carcinoma might be considered [46]. In addition, regional recurrence is not frequent, particularly in T1–T2 tumors [21, 23]. Conversely, local recurrence is the dominant failure and leading cause of mortality in patients with malignant neoplasms of the sinonasal tract in almost all reported studies. Distant metastasis at the time of diagnosis is rare and consists of less than 2% of all cases [23, 46]. However, distant failure alone or with local recurrence is more frequent and consists of 8–20% of all recurrent diseases [10, 23]. Figure 1 shows the pattern of local, regional, and distant failures of 1,024 recurrent diseases in the reported

Table 4 Characteristics and treatment results of 8,235 patients with malignant neoplasms of the sinonasal tract in major reported series

Author	No. of patients	Primary site	M/F ratio	Median age	Dominant failure	5-year LC (%)	5-year OS (%)	% of T3, T4, and/or N+	% of epithelial tumors
Betlejewski et al. [3]	927	PNS/NC	1.5	–	–	–	–	72	58
Bhattacharyya [4]	315	PNS/NC	1.7	66	Local	41	35	–	67
Blanch et al. [5]	235	PNS/NC	1.5	64	Local	–	30	–	66
Blanco et al. [6]	182	PNS/NC	1.9	–	–	–	30	90	80
Bristol et al. [9]	60	PNS/NC	4.5	65	Local	49	40	78	100
Calderon-Garciduenas et al. [10]	127	PNS/NC	5.3	58	Local	53	54	94	100
Cantu et al. [11]	109	PNS/NC	1.5	–	Local	63	62	72	100
Carrillo et al. [12]	73	PNS	4.2	57	Local	70	61	–	73
Chen et al. [13]	334	PNS	1.9	57	–	–	48	–	76
Fasunla and Lasisi [16]	168	PNS/NC	2.9	64	Local	62	35	87	74
Gadeberg et al. [17]	113	PNS/NC	2.3	68	–		–	72	79
Ganly et al. [18]	82	PNS/NC	2.2	44	–	–	–	86	91
Gao et al. [19]	259	PNS/NC	2.5	48	Local	59	65	–	56
Gil et al. [20]	78	PNS/NC	1.7	57	Local	60	50	45	90
Gras Cabrerizo et al. [21]	704	PNS	1.7	58	Local	56	46	67	78
Grau et al. [22]	167	PNS/NC	2.2	49	Local	–	44	–	68
Guntinas-Lichius et al. [23]	220	PNS/NC	1.6	58	Local	59	40	65	100
Haraguchi et al. [24]	87	PNS/NC	1.2	62	–	–	45	80	53
Harbo et al. [25]	109	PNS/NC	1.5	53	Local	–	40	91	100
Hicsonmez et al. [26]	106	PNS/NC	2.1	64	Local	58	27	–	100
Hone et al. [27]	60	NC	2.8	55	Local	–	48		43
Hoppe et al. [28]	265	PNS/NC	1.65	60	–	–	–	–	69
Howard et al. [29]	125	PNS/NC	3	58	Local	–	37	–	78
Hu et al. [30]	129	PNS	2.8	59	Local	–	–	60	100
Hu et al. [31]	43	PNS/NC	2.3	53	Local	50	45	–	–
Jakobsen et al. [32]	208	PNS	2.6	53	–	–	–	85	67
Jansen et al. [33]	783	NC	1.3	64	–	–	57	–	68
Jurkiewicz et al. [34]	256	PNS/NC	1	53	–	–	–	–	56
Katz et al. [35]	121	PNS/NC	1.8	–	Local	48	35	–	–
Krengli et al. [36]	73	PNS	2.2	–	Local	–	22	96	95
Logue and Slevin [37]	40	PNS/NC	–	–	Local	58	61	67	100
Lund et al. [38]	152	PNS/NC	–	–	Local	45	47	71	100
Madani et al. [39]	137	PNS	–	–	–	–	27	87	–
Mao [41]	127	PNS/NC	–	–	Local	62	52	–	100
Mendenhall et al. [42]	69	PNS/NC	–	–	Local	–	32	–	100
Porceddu et al. [48]	229	PNS	–	–	Local	64	41	–	100
Pres et al. [49]	85	PNS/NC	–	–	Local	62	67	–	–
Robin and Powell [50]	84	PNS/NC	–	–	–	71	58	–	89
Samant and Kruger [51]	317	NC	–	–	–	–	42	–	–
Samant et al. [52]	163	NC	–	–	–	–	58	–	–
Shah [53]	128	NC	–	–	–	–	42	–	–
Strohmann and Haake [57]	115	PNS/NC	–	–	–	–	41	–	–
Present study	71	PNS/NC	1	55	Local	59	54	70	65
Total	8,235	PNS/NC	1.8	57	Local	56	45.5	74.7	69[a]

[a] For this mean value, the studies including pure carcinomas [9–11, 23, 25, 26, 30, 35, 37, 38, 41, 42, 48] were excluded

Table 5 Distribution of the primary sites and histologic types of 5,798 patients in the literature review and 71 patients of the present study

The primary site and histologic type	Literature review (%)	Present study (%)
Primary sites		
Nasal cavity	34	29
Paranasal sinuses		
Maxillary sinus	38	41
Ethmoid sinus	25	27
Sphenoid sinus	2	3
Frontal sinus	<1	0
Histologic types		
Squamous cell carcinoma	36	27
Minor salivary glands		
Adenoid cystic carcinoma	9	25
Adenocarcinoma	16	4
Mucoepidermoid carcinoma	1	0
Others	2	0
Undifferentiated carcinoma	6	8
Lymphoma	4	10
Malignant melanoma	6	8.5
Esthesio- and olfactory neuroblastoma	8.5	8.5
Sarcomas	8.5	4
Transitional cell carcinoma	<1	1
Miscellaneous	2	4

series [9, 10, 12, 16, 19–21, 23, 25, 29, 47]. In our series, local recurrence was the most frequent treatment failure, although it was less dominant compared to most reported studies. The 5-year local control rate of our patients was 59.5%, which is comparable with 56% for 3,100 patients in the literature [4, 9–12, 16, 19–21, 23, 25, 31, 35, 37, 38, 41, 48–50]. In addition, the 5-year overall survival rate of our patients was 54.5%, which is higher than 45.5% for 6,184 patients in the literature [4, 5, 9–13, 16, 19–27, 31, 33, 35–42, 47–53]. There is an improvement in 5-year overall survival rate for the published series after the year 2000 compared to those before 2000 (47% vs. 40%), which may indicate a more effective treatment in recent decade [4, 5, 9–13, 16, 19–27, 31, 33, 35–42, 47–53].

Various potential prognostic factors affecting disease-free, local, and overall survival have been investigated in the literature. Advanced stage of disease, nonsurgical treatment, aggressive histologic type, and intracranial and orbital extension were independent prognostic factors and found to have a negative influence on survival in most reported series. Undifferentiated carcinoma, malignant melanoma, and squamous cell carcinoma were associated with greater morbidity and poorer survival compared to favorable histologic types such as adenoid cystic carcinoma and adenocarcinoma. On the other hand, surgery and postoperative radiotherapy have been found to improve local control and survival when compared with radiotherapy alone [4, 10, 11, 13, 16, 19, 20, 22, 23]. Few reports found primary site, age, and surgical margin status as a prognostic factor in patients with malignant neoplasms of the sinonasal tract [4, 13, 16, 23, 54]. In the present study, on multivariate analysis, only response to therapy and stage of disease were independent prognostic factors.

The optimal treatment for patients with malignant neoplasms of the sinonasal tract remains to be defined, however; craniofacial or endoscopic resection followed by postoperative radiotherapy is currently considered for the vast majority of patients with locally advance disease or aggressive histologies [7, 11, 19, 22, 53, 55]. Consistent with the results of our study, in most studies, surgery followed by postoperative radiotherapy was the most frequent treatment modality used in these patients [3, 6–9, 12, 13, 16, 17, 20, 23, 25, 26, 41, 48, 54–58]. For overcoming local failure, a more aggressive combined approach including craniofacial resection followed by radiotherapy using modern radiation techniques, such as intensity-modulated radiotherapy, is suggested by some authors [9, 12, 13, 16, 50, 59]. There are increasing evidences that the use of concurrent chemo-radiation, in particular with cisplatin-based regimens, can improve outcome in patients with locally advanced head and neck carcinomas [60–62].

In conclusion, despite some improvement in overall survival of patients with malignant neoplasm of the sinonasal tract in the recent decade, the outcome remains moderate to poor. This review suggests the need for a more effective local and systemic treatment in these neoplasms.

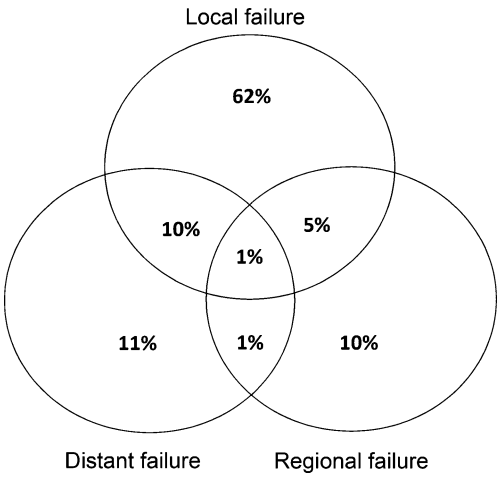

Fig. 1 The pattern of local, regional, and distant failures of 1,024 recurrent diseases

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