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Value of regional lymphadenectomy in pancreatic cancer

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Abstract
Radical surgical resection and adjuvant chemotherapy are the goal standard to attempt significant long term survival in patients suffering from ductal pancreatic cancer. The role of extended lymph-node dissection is still a debated issue. In this paper a deep review of the experiences reported in the literature is carried out. Several studies are limited, not randomized and retrospective: generally speaking they seem to suggest a positive role in node dissection. Unfortunately, this trend is not confirmed in the only two trials conducted in a prospective and randomized setting. Moreover the results of these studies are also difficult to compare. At the moment we can say that extended lymphadenectomy does not play a determinant role for long term survival but a positive trend has been shown for node positive patients.

The only realistic chance of a cure for patients suffering from ductal pancreatic cancer of the pancreas is the radical resection of the tumors.

In the past, the disappointing results achieved in the overall long-term survival of resected patients appeared to prompt many surgeons to refrain from surgical intervention [1].

What we have actually witnessed over the years is a progressive increase in resection rates, which have steadily risen from around 20% some 15–20 years ago to an average of 35% of cases observed today and which now even exceed 50% in some centers [2]. Moreover the tempting results on long-term survival rate recently achieved by adjuvant treatment in a large multi-center randomized study further support the need of aggressive behaviour [3,4]. Today we believe that in cases in which the preoperative staging has ruled out both remote metastases and loco-regional, not resectability, it is ethically mandatory to regard 'taking it out' (plus adjuvant chemotherapy!) as the primary aim of curative treatment of carcinoma of the pancreas; this seems to be the suggested and correct policy to use in those centers where the morbidity (around 30%) and mortality rates (<5%) make this a feasible and reasonable proposition.

The 'N' factor

Unfortunately the staging of the N factor can be completely clarified only after surgical resection, and the reliability of lymph-node negativity is directly related to the extent of the performed lymphadenectomy and to the pathologist care in the specimen analysis. Moreover, there is a frequent lack of correlation between tumor diameter and lymph-node positivity, which, in some case series, may be present in as many as 50% of cases of small tumors (T <2 cm) [5]. The risk of false-negatives also results in the lack of anatomical contiguity in the lymphatic invasion pattern of the pancreatic cancer, with possible positivity in remote lymph-node stations together with negative peripancreatic lymph nodes. The result of this behavior of N factor and the lack of any correlation between N positivity and precise 'evidence based' adjuvant options, is that the effective need for a more or less extended lymphadenectomy accompanying the take-out in carcinoma of the pancreas remains a hotly debated issue.

Looking at the frequency and pattern of lymph-node involvement in pancreatic cancer, it can be noted that the rate of resected patients with lymph-node

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involvement is around 70% [1–41]. The more aggressive approach adopted in Japan might be thought to lead to a generally higher incidence of lymph-node positivity in case series in the Far East. Surprisingly the percentage distribution shows no significant difference on the basis of this parameter: the figure reported by the Japan Pancreas Society (74.6% positivity) [6] is comparable to the rates reported in European [7] and American [8] studies (67.5% and 71.6%, respectively). In our own more recent series of 100 patients undergoing pancreaticoduodenoctomy for ductal carcinoma, 67 were lymph-node positive (unpublished data).

Particularly interesting, in this connection, are the studies conducted by Cubilla and Fitzgerald [9], which show that the standard Whipple successfully removes 80% of the lymph-node sites most commonly involved. Apart from this study, the literature contains very few reports of pathological analyses of surgical specimens aimed at establishing the topographical distribution of the lymph-node areas affected by the tumor spread [5,10,11].

In this sector, the Japanese literature is by far the most informative, thanks above all to Nagakawa's study [5], which was planned with the intention to assess, on the basis of quantitative evidence, whether lymphadenectomy should be also extended to the remote lymph nodes: 68.6% of patients presented lymph-node metastases, and 73.7% of these lymph-node-positive subjects showed simultaneous positivity of the resection margin of the posterior lamina. Also looking at our already stressed most recent experience on 100 consecutive patients, the rate of R1 and R2 with N positivity is similar (67.5%). The lymph-node areas most affected are similar too: area 13 (posterior to the head of the pancreas), 17 (anterior to the head of the pancreas) and 14 (radix of the mesenteric area), followed by areas 12 (hepatoduodenal ligament) and 16 (along the abdominal aorta).

All other sites are only sporadically affected. In particular, in area 16 the highest incidence is in the interaortocaval region.

The extent of lymphatic metastasis tends to increase with tumor diameter, though the finding in two of Nagakawa's cases [5] of small tumors (diameter <2 cm) which had already metastasized to area 16 provided evidence of a poor correlation with bizarre involvement and distribution of the N factor as compared to the T factor. This unpredictability is further confirmed by our own experience: in a study aimed at detecting small tumors of the pancreatic head [12], none of the 4 cases prospectively identified out of 72 consecutive observations were N+. By contrast, 3 out of 7 small tumors identified retrospectively in 56 historical patients were N+; even one of the more recent cases with lymph-node positivity had a diameter of 1.5 cm. Taken together all these data would appear to suggest that the pathway of para-aortic metastases passes via a retroperitoneal lymphatic route from area 13 to area 14 before reaching area 16.

On the basis of his analysis, Nagakawa concludes that 'an extensive dissection including areas 14 and 16 is necessary for radical resection' [5].

Non-performance of a standard lymphadenectomy in all patients, in Western series, might be interpreted as the result of both a non-homogeneous surgical approach and definitions used for the standard and extended procedures by the Western surgeons. In actual fact, we surgeons often find ourselves having to operate on patients who, despite the disease, present a major intra-abdominal lipid component of a type which, for anthropomorphic and dietetic reasons, is comparatively rare in Eastern populations. This technical obstacle often proves insurmountable except by prolonging the related operative times and risks, at least in theoretical terms.

For this reason, our recent series included only 15 N+ cases potentially capable of providing data on the ill-famed area 16. Two patients presented positivity in this area, both of which in lymph nodes of interaortocaval origin. The similarities to Nagakawa's findings [5], in terms of both frequency and site, are suggestive.

In one of our two cases, sequential involvement of areas 13 → 14 → 16 was observed, whereas in the other the area 16 positivity coincided with positivity only of area 13, all the other areas yielding negative findings. The erratic pattern of lymph-node involvement is also confirmed by two cases which were lymph-node negative in area 13, but positive at the level of the hepatoduodenal ligament (area 12): one of these tumors had a diameter of 1.5 cm (the above-mentioned small N+ tumor) and the other a diameter of 4 cm.

Despite these incongruities, which make any correlation between N and T factors unreliable, in our case series, too, the mean diameter of the N− tumors was less than that of the N+ malignancies (26.3 mm, with a range from 10 mm to 40 mm; and 30.5 mm, with a range from 15 mm to 40, respectively).

The 'N' factor and the prognosis

Despite the generally widespread conviction that the presence of lymph-node metastases is a highly prejudicial factor for the prognosis of pancreatic carcinoma, this is by no means an established fact in the literature [1–41]; several studies fail to tackle the issue on the basis of multivariate-type analysis, leaving the reader with the suspicion that some other co-factor potentially capable of affecting the prognosis may to some extent blur the real significance of lymph-node positivity.

An elegant study by Cameron *et al.* [13] showed, however, that, in multivariate analysis, too, the strongest predictive factor is lymph-node status with a median survival of 55.8 months in N− patients as against 11 in N+ subjects. In 1995, the same group [8] substantially confirmed the findings for lymph-node status, associating it, additionally, with tumor diameter