Diagnostic and treatment modalities in carcinoid tumours

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General introduction

Metastatic carcinoid tumors: a clinical review

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General introduction

Introduction and epidemiology:

Carcinoid tumours were first described in 1888 by Lubarsch, who found multiple tumours in the distal ileum of two patients at autopsy. The term “karzinoide tumoren” was first used in 1907 by Oberndorfer to describe a similar tumour which was morphologically distinct and less aggressive in behaviour than classical adenocarcinomas. Carcinoid tumours are neuroendocrine tumours derived from enterochromaffin or Kulchitsky cells which are widely distributed in the body. For this reason they may be found at any location in the body, but they are traditionally described as originating from the foregut, midgut and hindgut.3

The annual incidence rate of carcinoid is around 2 cases per 100,000 inhabitants and varies with gender, age and race. However, in autopsies the incidental finding of these tumours is much higher (up to 0.5-1%) with the main location in the small intestine.4,5 Carcinoids appear to have an increased overall incidence in the past decades6-8, possibly as a result of changes in detection rate.9 In the age-specific incidence rates a peak between 15-25 years and another between 65-75 years can be found. Under the age of 50 years the incidence is approximately twice as high in females compared with men. At higher ages a male predominance is observed with a doubled rate for men compared to women.9,10 For all sites, age-adjusted incidence rates are higher in black males (4.48 cases per 100,000 people).6

The sites most often affected in carcinoids are the gastrointestinal tract (about 65%) followed by the bronchopulmonary tract (about 25%). In about 10% the primary tumour remains unknown. Presentation with distant metastases is found in 22%, half of those with unknown primaries.

Overall 5-year survival rate for all carcinoid tumours (regardless of site or stage) is 70-80%.6,8,10 As might be expected, stage of disease influences the prognosis significantly with the best 5-year survival in localised disease (93%) and a poor 5-year survival in distant metastatic disease (20-30%). The best overall 5-year survival rates are observed in patients with appendiceal and lung carcinoid tumours (95 and 80% respectively) due to a low rate in invasive growth or metastatic spread.

Survival has improved over the last decades.6,7,10 In a study of Quaedvlieg et al.10 the introduction of octreotide therapy was suggested to be a factor in the improvement of survival in patients with metastatic disease.

Hereditary predisposition:

Information about risk factors in carcinoid tumours is scarce and most carcinoids are assumed to be sporadic. In a minority of patients with a carcinoid tumour, there is a
relationship with the multiple endocrine neoplasia type 1 (MEN-1). This is an autosomal, dominantly inherited disorder, with the MEN-1 gene localised on chromosome 11 (11q13). The classical syndrome includes neoplasia of the parathyroid glands, pancreas, anterior pituitary and neuroendocrine tumours of the lungs, thymus and stomach (foregut).\(^{11-13}\) A family history of carcinoid tumours is reported in less than 1% of the patients and some case reports have been published on this subject.\(^{14-17}\) However, the relative risk of developing a carcinoid tumour in an individual with one affected first-degree relative is 3.6 (95% CI 3.3-4.1) and with two affected offspring more than 12 (95% CI 3.2-27.4).\(^{9,18,19}\) A study performed in familial pulmonary carcinoid tumours not associated with MEN-1, did not reveal a specific genetic disorder\(^{20}\), although lung carcinoids are more prone to have deletions on chromosome 11q. In sporadic midgut carcinoids a high frequency in deletions of chromosome 18 is described.\(^{21}\) These findings might indicate different pathways in development for carcinoids from foregut and midgut.\(^{22,23}\)

**Histology and classification:**

In the last decades several classification systems for endocrine tumours have been applied. In 1980 the WHO classification of endocrine tumours applied the term “carcinoid” to all tumours of the diffuse neuroendocrine system, excluding islet cell tumours, medullary carcinoma of the thyroid, paraganglioma, small cell lung cancer and Merkel cell tumours of the skin. Subdivision in carcinoids was made on the basis of various silver and other staining techniques. In the following years this classification system was overtaken by the development of more detailed immunohistochemical testing methods and a growing demand for a classification focused on prognostic histological features. Probably the most useful classification to predict prognosis of neuroendocrine tumours originating from the gastro-intestinal tract, is the revised classification of neuroendocrine tumours of the lung, pancreas and gut by Capella et al.\(^{24}\) In this classification tumours are graded as: benign, low-grade malignant and high-grade malignant. The criteria used in this subdivision are histological differentiation, tumour size, angioinvasion, and infiltrative growth. This is combined with the primary tumour site and production of hormones. Histological features related to prognosis in pulmonary neuroendocrine tumours are described in a study of Travis et al.\(^{25}\) A combination of morphology, mitotic index and necrosis proved to be useful in the prediction of prognosis. An attempt to improve the prognostic power of the classification system was made by Van Eeden et al.\(^{26}\) who investigated whether a combination of both systems resulted in a fine-tuning of the prediction of prognosis of midgut tumours and unknown primaries. Subdivision of these low-grade tumours appeared to be of less value compared to this
subdivision in neuroendocrine tumours of the lung. In this thesis the term “carcinoid” was used to indicate low-grade neuroendocrine tumours of the foregut, midgut and hindgut.

Pathophysiology and serotonin metabolism

Depending on their site of origin, carcinoid tumours can have the ability to secrete vasoactive peptides. Serotonin production is the most prominent, especially in midgut tumours. However, 5-hydroxytryptophan (5-HTP), bradykinins, tachykinins, histamine, substance P, ACTH and several other peptides are also reported to be produced by carcinoids.

Under normal conditions about 99% of dietary tryptophan is metabolised by the oxidative pathway into nicotinic acid, and less than 1% is converted into 5-HTP. In carcinoid tumours a disequilibrium of tryptophan metabolism results in 5-hydroxylation of most of the tryptophan with the production of large quantities of 5-HTP, serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA).\(^{27-29}\) If there is a deficiency in aromatic amino acid decarboxylase in carcinoid tumour cells, conversion of 5-HT in serotonin will not occur and the tumours excrete 5-HT instead of serotonin.\(^{30}\) Due to this shift a reduction in nicotinic acid pools can cause pellagra in carcinoid patients.\(^{31-33}\) Urinary 5-HIAA, the breakdown product of serotonin, is still an important marker for carcinoid tumours.

![Pathophysiology and serotonin metabolism diagram](image-url)
Clinical presentation and complications

Carcinoid tumours have a relatively slow growing pattern and even in the presence of metastatic disease patients can survive for several years. Unless secretory products are directly secreted in the systemic circulation, systemic signs and symptoms are usually not present. Paracrine secretion of hormonal products in the intestine can cause diarrhoea. If there is a release of vasoactive peptides in the systemic circulation (in case of liver metastases or e.g. bronchus carcinoid tumours) patients often present with the characteristic symptoms of the carcinoid syndrome, such as diarrhoea, flushing and less frequently wheezing. Overproduction of serotonin seems to cause the complaints of diarrhoea. The correlation between serotonin production and symptoms of flushes is not convincing and probably other hormones like tachykinins are of importance in the pathogenesis of this symptom. The cause of wheezing is less clear. It has been supposed that the release of histamine and serotonin can play a role in this symptom, but clear evidence is not found in literature.

Carcinoid heart disease (CHD) is a late complication and occurs in 20-70% of the patients with metastatic carcinoid tumours. In many patients the cause of death is attributed directly to the cardiac disease. The pathogenesis of carcinoid heart lesions has not yet been fully elucidated, but serotonin plays an important role. This is supported by the finding of similar valve lesions in patients using appetite-suppressants, such as fenfluramine or dexfenfluramine, and anti-migraine drugs, such as ergotamin and methysergide, agents which all act via the serotonin pathway.

In several studies urinary 5-HIAA excretion, being indicative for the amount of serotonin production, was significantly higher in patients with carcinoid heart disease compared with those without. Not only a high serotonin level, but also the duration of exposure to serotonin is important in the development of CHD.

Carcinoid crisis with severe flushes and diarrhoea leading to dehydration, hypotension and arrhythmias, along with unconsciousness is a potential life-threatening complication. It might be provoked by anaesthetic of invasive procedures and is probably caused by an excessive release of vasoactive peptides into the circulation. Therefore, it is important that prophylactic measures (such as continuous intravenous octreotide infusion and extra hydration started simultaneously with the intervention) are taken during these procedures to prevent a carcinoid crisis.

In a substantial number of patients the primary tumour remains unknown despite extensive diagnostic investigations. However, primary tumours in the small bowel can cause complications such as bowel obstruction or fibrosis with shrinkage of the mesentery during follow-up. Due to mesenterial fibrosis patients can suffer from disabling abdominal pain with malnutrition and kinking of the bowel. Additionally, fibrosis can lead to intestinal ischaemia with finally necrosis and perforation of the bowel wall.
Metastases to the skin seem to be a late manifestation of advanced disease, but data in the literature are scant and limited to single case reports only. These metastases may present as painless subcutaneous nodules, but sometimes they are extremely painful. The pathogenesis of the severe pain encountered in these often tiny metastatic deposits remains difficult, as neural involvement is not a consistent finding. Pain can be difficult to manage with analgesics, but local excision demonstrated to provide satisfactory long-term palliation.

The incidence of skeletal metastases in neuroendocrine tumours has been reported to be approximately 10%. Although bone metastases arise more often from bronchial or hindgut primaries compared to midgut carcinoid tumours, recent studies show no preferential primary site. The axial skeleton is the most commonly affected site. Bone scintigraphy is the most sensitive nuclear imaging technique to detect bone metastases in carcinoid disease compared to In-pentetreotide and metaiodobenzylguanidine (MIBG) scintigraphy. Pain is the main symptom of bone metastases and radiotherapy provides satisfactory long-term palliation in majority of patients.

Diagnosis

Pathology:
In most patients the diagnosis is based on tissue examination, mostly a biopsy from a liver metastasis. However, in some patients attempts to collect histologic material can fail and in these cases diagnosis can be based on symptoms combined with radiologic and scintigraphic findings. The biopsy material should be examined by a pathologist familiar with the diagnosis carcinoid to prevent confusion with an adenocarcinoma with neuroendocrine markers. Depending on the presence of necrosis and/or mitosis, tumours can be graded as: low-grade malignant and high-grade malignant, which is useful in the prediction of prognosis.

Tumour markers:
Urinary 5-HIAA, the breakdown product of serotonin, has been the golden standard for diagnosis and follow-up of carcinoid patients for many years. The specificity of this determination is almost 100%, but the sensitivity is reported to be much lower (35%). Urinary 5-HIAA levels can be influenced by food (e.g. bananas, avocados, pineapple and walnuts) and medication. Platelet serotonin level is a more sensitive marker for the detection of small amounts of serotonin. However, in cases with a high rate of serotonin excretion, serotonin in platelets
reach a maximum and can no longer be used for a quantitative determination and hence evaluation during follow-up.\textsuperscript{70,71}

Chromogranin A (CgA) is an acidic, hydrophilic protein of 49 kDa present in the chromaffin granules of neuroendocrine cells. In contrast to urinary 5-HIAA levels and platelet serotonin it can be used in the detection of functioning as well as non-functioning tumours. Although specificity is lower compared to urinary 5-HIAA levels (86 and 100\% respectively), the sensitivity is much higher (35 and 68\% respectively).\textsuperscript{67} and reported to be the highest in foregut and functioning tumours.\textsuperscript{72} Levels of CgA are correlated to tumour burden\textsuperscript{72,73} and a direct comparison between serum CgA and urinary 5-HIAA levels showed a higher accuracy of CgA for the detection of a relapse in carcinoid patients.\textsuperscript{74} A significantly worse survival is described in patients with very high levels of CgA (> 5000 \(\mu\)g/L).\textsuperscript{75} Data concerning the value of CgA in the follow-up of carcinoid patients to monitor treatment effects is scarce and limited to small series.\textsuperscript{72,76,77}

\textit{Nuclear scintigraphy:}

\textsuperscript{111}In-pentetreotide scintigraphy (Octreoscan®):

Somatostatin receptors (SSR) are located on the cell membrane of carcinoid tumours (especially subtype 2 and 5). Octreotide analogues have a high affinity for the SSR 2 and 5 and a much lower binding to the SSR 1, 3 and 4.\textsuperscript{78} \textsuperscript{111}In-pentetreotide (a radioactive labelled octreotide analogue) shares the receptor-binding profile of octreotide, which makes it a good radiopharmaceutical for the imaging of carcinoid tumours.\textsuperscript{79} The sensitivity of this scintigraphy has been reported to be 80-90\%.\textsuperscript{80,81} Apart from information about the localisation of the tumour, a positive octreoscan also predicts response to octreotide therapy.\textsuperscript{82}

\textsuperscript{131}I-meta-iodobenzylguanidine (MIBG) scintigraphy (MIBG-scan):

\textsuperscript{131}I-MIBG is an analogue of a biogenic amine precursor and is taken up by chromaffin cells and stored in the neurosecretory granules. Using \textsuperscript{131}I-MIBG for the detection and imaging of neuroendocrine tumours was reported in the 80’s\textsuperscript{83} followed by papers about therapeutic applications of \textsuperscript{131}I-MIBG.\textsuperscript{84-86} The sensitivity of the MIBG-scan is reported to be a little lower compared to the octreoscan (70 vs. 85\%).\textsuperscript{81} However, a direct comparison between these two modalities showed comparable results with a sensitivity of about 84\%.\textsuperscript{80,87} A combination of these scans increases the sensitivity to 95\%.\textsuperscript{80}

\textit{Bone scintigraphy:}

Although \textsuperscript{111}In-pentetreotide scintigraphy and the \textsuperscript{131}I-MIBG scintigraphy are positive in 70-80\% in carcinoid tumours, in the detection of bone metastases these scans are only positive in 50\% and 20\% respectively.\textsuperscript{61} Bone scintigraphy has a high sensitivity for the
detection of these metastases of 90-100% and can be used in patients with the suspicion of bone metastases.  

Positron emission tomography (PET):
PET scanning using [18F]fluoro-deoxy-glucose (FDG) is widely used as a powerful imaging technique in clinical oncology. Unfortunately, increased FDG uptake in carcinoid tumours is limited due to the low proliferative activity and high differentiation. Therefore, several tracers directed towards the specific characteristics of carcinoid tumours like 6-[18F]fluorodopamine (18F dopa) and 5-hydroxy-L-tryptophan (5-HTP) were developed for PET imaging in these tumours. Although the availability of PET scanning for the clinical diagnosis of carcinoid tumours is still limited, promising results have been described in diagnosing small lesions and lymph node metastases with a sensitivity of up to 65% for the 18F dopa PET.

Apart from the role in staging of carcinoid tumours, uptake of 5-HTP as a tracer in PET scanning is also of value in follow-up and therapy monitoring.

Radiography:
Computerised tomography scan (CT-scan) can be used for visualizing liver metastases, extra hepatic tumour localisation in the abdomen (lymph nodes, mesenterial tumour deposition) and localisation in mediastinum and lungs. In addition to follow-up, the findings on CT-scan can also be applied for decision making of local treatment options like resection of metastases in the liver and mesenterium or radiofrequency ablation of liver metastases.

Primary tumours in the small bowel can be demonstrated with barium follow-through although small primaries are easily missed by this technique.

Video capsule endoscopy:
Video capsule endoscopy is a new promising technique for the visualization of the mucosa of the small bowel. The first reports on application in patients with small bowel bleeding are promising and results are better compared to push endoscopy. In the diagnosis of Crohn’s disease this technique seems to be superior to barium follow-through and CT-scan. Experience with the application of the video capsule in carcinoid patients is limited, but the detection of primary carcinoid tumours in the small bowel and early resection is a potential indication for this technique.

Cardiac evaluation:
Detection of carcinoid heart disease in an early stage is important to adjust therapy and hence improve prognosis. Echocardiography in the follow-up and monitoring of carcinoid patients is the cornerstone for the detection of valvular lesions. However, performing an
Echocardiography is laborious, expensive and not always readily available as referral to a cardiologist is necessary. A new development is the detection of cardiac damage by using natriuretic peptide (e.g. brain natriuretic peptide, BNP) levels in blood. A regular screening of BNP levels might direct the use of cardiac ultrasound and guide treatment strategies.  

Treatment

Supportive care:
As quality of life is severely impaired in patients suffering from the carcinoid syndrome with flushes and diarrhoea, supportive care in these patients is essential. Flashes can be reduced by avoiding stress and foods known to provoke symptoms (e.g. alcoholic beverages, spicy meals). Diarrhoea can be treated with simple anti-diarrhoeal medications, such as loperamide and codeine. Severe diarrhoea can lead to vitamin deficiencies and due to the extensive production of serotonin, a depletion in nicotinic acid can occur which can cause pellagra. Supplementation of vitamins and nicotinic acid is recommended.

Octreotide analogues:
Somatostatin interferes with the release of hormones and neurotransmitters through activation of membrane receptors. It's short half-life (2-4 minutes) limits the clinical application. Octreotide, a somatostatin analogue, has a half life of 90-120 minutes and can be administered subcutaneously every 6-8 hours. Octreotide can induce symptomatic improvement in up to 80% of patients, although a good clinical response is not always reflected by a reduction of 5-HIAA excretion in urine, as biochemical response is present in 70%.  

A positive "In-pentetreotide scintigraphy may be predictive for a clinical response to treatment with somatostatin analogues. A major disadvantage is the need for subcutaneous injections twice (or sometimes thrice) daily. This drawback may be overcome by slow-release preparations (one intramuscular injection per 2-4 weeks). In addition to improvement of symptoms, somatostatin analogues have also been reported to inhibit tumour growth. However, reduction in tumour volume is only occasionally observed.

Interferon-α:
Interferon (IFN) has been introduced in 1982 as a treatment modality for carcinoid tumours. Although IFN is now widely used in the treatment of carcinoid tumours, the exact mechanism of actions is not yet understood. Possible mechanisms are inhibition of cell proliferation, immune cell mediated cytotoxicity, inhibition of angiogenesis and
reduction in tumour growth by blocking the cell cycle. The biochemical and subjective responses are reported in respectively 40 and 70% of the patients. A reduction in tumour size is reported in a small minority of patients (about 10-20%) and administration of higher dosages of IFN does not increase this response number. Development of antibodies during treatment with IFN is described in about 5-20% of the patients and seems to be higher with the use of interferon-α 2A (Roferon®) compared to interferon-α 2B (Intron-A®). The role of these antibodies is controversial. Studies in patients with hepatitis B or C did not reveal a relationship between antibody development and therapeutic response. However, in a study among 327 carcinoid patients high titres of antibodies were associated with a failure of response to treatment, but this phenomenon occurred late in the disease after a median of 25 months. A synergism in antiproliferative effects of the combination of octreotide and IFN was reported earlier. However, in a recent published prospective study of Fais et al. there were no differences in response rates by comparing a combination of octreotide and IFN with either therapy alone.

Meta-iodobenzylguanidine (MIBG): Using a tracer dose of 131I-MIBG for the detection and imaging of neuroendocrine tumours was reported in the 80's followed by papers about therapeutic applications of a higher dose 131I-MIBG. MIBG is a biogenic amine precursor which resembles noradrenaline. Due to its high affinity for the noradrenalin transporter protein, it is taken up by chromaffin cells and stored in neurosecretory granules. Although about 70% of carcinoid tumours are MIBG-avid, tumour uptake is not always sufficient for therapy. Various applications of MIBG can be used in the treatment of carcinoid patients. Apart from its help in tumour imaging, successful treatment of carcinoid tumours with 131I-MIBG was described in a small series of patients in 1987. 131I-MIBG was applied in a much higher dose (200 mCi=7.4 GBq) to provide a selective local effect by internal radiation in the tumour cells in patients with a positive 131I-MIBG scan. Significant symptomatic responses were reported in 60% of the patients with a duration of 8 months in a prospective study of Taal et al. The main disadvantage of this treatment is the need for isolation as legally required. Application of unlabelled MIBG was reported in 1996; in carcinoid patients it resulted in symptomatic responses in 60% of the patients with a short median duration of 4-5 months. The cytotoxic effect of unlabelled MIBG is related to inhibition of mitochondrial respiration and is dependent on anaerobic glycolysis, resulting in enhanced glucose consumption, increased lactic acid production, inhibition of oxygen consumption and decreased adenosine triphosphate levels. Finally, the radioactive ("hot") MIBG after predosing with the unlabelled ("cold") MIBG resulted in improved biodistribution with more intense MIBG uptake in the tumour. In addition, more patients were eligible for the radioactive treatment after predosing.
Radioactive labelled somatostatin analogues:
The somatostatin analogue octreotide has been used since the nineties for imaging and treatment of carcinoid tumours. Recently several radioactive labelled somatostatin analogues have been developed for application in neuroendocrine tumours with a positive $^{111}$In-pentetreotide scintigraphy. $^{111}$In-pentetreotide has a limited radiation range and is suitable for treatment of small tumours or micrometastases. However, clear tumour reduction is only reported in a minority of patients while symptomatic improvement is observed more frequently.$^{119-121}$ Side-effects are mild and restricted to minor haematological toxicity and renal function impairment.$^{122}$ Higher tumour radiation can be achieved by application of $^{90}$Y and $^{177}$Lu which are β-particles with a wider range of radiation and possibly a higher tumour uptake in neuroendocrine tumour lesions.$^{123}$ First reports of these modalities show a tumour reduction in about 15-30% of the patients with clinical benefit up to 60%.$^{124-128}$ Observed toxicities are nausea and vomiting, haematological toxicity and some renal function impairment. However, there are some papers reporting development of end-stage renal failure or myelodysplastic syndrome/leukaemia after application of radioactive labelled somatostatin analogues.$^{129;130}$

Systemic chemotherapy:
The indication for chemotherapy in neuroendocrine tumours is limited and it is reserved for the high-grade malignancies, which represent only a small minority in this tumour group. Single-agent chemotherapy is not very useful in the treatment of carcinoid tumours due to the very low response rates of about 5-10%.$^{131}$ Although schedules with a combination of chemotherapy have a slight better response rate (15-30%), these results are still disappointing.$^{132-135}$ A direct comparison between IFN and chemotherapy did not result in a better response with the application of chemotherapy.$^{136;137}$ Therefore, chemotherapy is not considered to be the first line of treatment in carcinoid tumours.

Hepatic artery (chemo) embolisation (HA(C)E):
Local treatment of hepatic metastases of carcinoid is attractive because of the slow and localised growth pattern. Liver metastases are usually diffuse at the time of diagnosis, and surgical resection is rarely feasible. Hepatic artery embolisation (HAE) is a local treatment modality of the liver, which not only may ameliorate symptoms but also might reduce tumour burden. An objective or biochemical response up to 50% and a median duration of effect of 12 months have been reported in cases of failing systemic therapy.$^{138;139}$ Reports on chemoembolisation show a slightly better biochemical and tumour response.$^{140;141}$ Side-effects are pain in the liver region, renal toxicity and elevation of liver enzymes with fever (post-embolisation syndrome).

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Radiofrequency ablation (RFA):
Radiofrequency ablation (RFA) is a fairly new technique which can be used in case of nodules up to 4 cm diameter in the treatment of unresectable primary and secondary hepatic tumours. The complication rate is 5-10% and the mortality rate is low with a reduction in complications with increasing experience with this technique. Application of RFA in metastases of neuroendocrine tumours has been reported in small series. Local tumour control is reported in almost all patients and a symptomatic and biochemical response in about 60-80% of the patients. However, local recurrence and development of new metastases is frequently reported.

Conclusions:
Prognosis of metastatic carcinoid tumours has improved during the last decade. Due to a longer survival, complications such as carcinoid heart disease and new metastatic patterns like skin and bone metastases may become a more important feature in carcinoid disease. Follow-up should be focused on monitoring tumour size and extension of metastases by CT-scan and nuclear scanning. Special attention should be given on unexpected metastatic patterns like bone metastases. As survival is poor in patients with carcinoid heart disease treatment should be focused on reducing elevated levels of hormonal excretion even if there are no symptoms of the carcinoid syndrome. During follow-up hormonal activity has to be monitored on a regular basis. Routine examinations every 6-12 months to detect carcinoid related heart disease in an early stage is important to adjust therapy and hence improve prognosis. Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in a better quality of life and a longer survival. The increasing number of therapeutic options and diagnostic procedures requires a multidisciplinary approach with a team consisting of an oncologist, surgeon, pathologist, gastroenterologist, cardiologist, radiologist and nuclear medicine. Decisions should be made in multidisciplinary meetings focused on “tailor-made” therapy based on patients’ specific conditions.
References


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